








h.s.  
v.7-8.

Library  
of the  
Academy of Medicine  
Toronto.

17197

Presented by

*The Society*  
1925



Digitized by the Internet Archive  
in 2010 with funding from  
University of Toronto





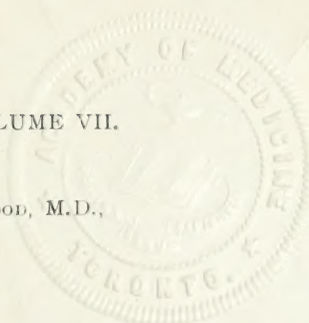
PROCEEDINGS  
OF THE  
NEW YORK PATHOLOGICAL  
SOCIETY.

---

NEW SERIES, VOLUME VII.

1907

FRANCIS CARTER WOOD, M.D.,  
Editor.



LIST OF OFFICERS AND COMMITTEES FOR THE  
YEAR 1907.



*President:*

DR. CHARLES NORRIS.

*Vice-President:*

DR. E. LIBMAN.

*Secretary:*

DR. KARL M. VOGEL.

*Treasurer:*

DR. GEORGE C. FREEBORN.

*Editor:*

DR. FRANCIS CARTER WOOD.

*Committee on Admission and Ethics:*

DR. HARLOW BROOKS.

DR. CHARLES NORRIS.

DR. E. LIBMAN.

DR. HORST OERTEL.

DR. AUGUSTUS WADSWORTH.

*Committee on Publication:*

DR. AUGUSTUS WADSWORTH.

DR. E. LIBMAN.

DR. FRANCIS CARTER WOOD,

*Editor.*

DR. GEORGE C. FREEBORN,

*Treasurer.*

DR. KARL M. VOGEL,

*Secretary.*



# I N D E X.

---

	PAGE
<i>Acromegalia, Case of</i> —Norris .....	119
<i>Adrenal Gland, Hypernephroma of</i> —Satterlee .....	171
<i>Agglutination, Phenomena of</i> —Field .....	35
<i>Ambœ in Mouths of Healthy Individuals</i> —Le Wald .....	219
<i>Anemia due to Bothriocephalus latus</i> —Lynah .....	91
<i>Angiosarcoma of Foot</i> —Satterlee .....	171
<i>Arteries, Calcification of, in Cat</i> —Carrel .....	199
<i>Arteriosclerosis of Pulmonary Vessels</i> —Brooks .....	177
 <i>Bacillus aerogenes capsulatus, Sporulation of</i> —Noguchi .....	196
<i>Bacillus typhosus, Peritoneal Infection by</i> —Zinsser ... ..	165
<i>Bath, Desk, for Opsonic Work</i> —Wadsworth .....	129
<i>Bierwirth, J. C., and Brooks, H.—Case of Streptococcus Sepsis</i> .....	93
<i>Blastomycosis, Case of</i> —Brewer .....	54
<i>Blastomycotic Lesions, Experimental</i> —Zinsser .....	121
<i>Bothriocephalus latus, Case of Anemia due to</i> —Lynah .....	91
<i>Breasts, Case of Diffuse Bilateral Hypertrophy of Female</i> —Ward .....	156
<i>Brewer, G. E.—Case of Blastomycosis</i> .....	54
<i>Brooks, H.—Case of Arteriosclerosis of Pulmonary Vessels..</i>	177
Experimental Study of Caisson Disease .....	58
<i>Brooks, H., and Bierwirth, J. C.—Case of Streptococcus Sepsis</i> .....	93
 <i>Caisson Disease, Experimental Study of</i> —Brooks .....	58
<i>Calcification of Arteries in a Cat</i> —Carrel .....	199
<i>Carrel, A.—Calcification of Arteries in a Cat with Transplanted Kidneys</i> .....	199
<i>Celler, H. L., and Libman, E.—Case of Chronic Suppurative Lymphadenitis and Pylephlebitis</i> .....	139
<i>Compression Paraplegia, Case of</i> —Gibney .....	102
<i>Cystitis Cystica, Case of</i> —Schultze .....	212

<i>Decidual Reaction in Ectopic Pregnancy</i> —Wood.....	136
<i>Diphtheritic Laryngitis, Tracheitis and Bronchitis, Case of</i> — Flournoy .....	213
<i>Ductus Thoracicus, Tuberculosis of</i> —Weil.....	211
<i>Dysentery, Mid-Winter Epidemic of</i> —Zinsser.....	162
<i>Ectopic Pregnancy, Decidual Reaction in</i> —Wood.....	136
<i>Endarteritis obliterans, Case of</i> —Levin.....	213
<i>Esophagus, Case of Rupture of Cardiac Orifice of</i> —Schultze.	138
<i>Ewing, J.</i> —Involution Forms of <i>S. pallida</i> in Gumata .....	166
<i>Fetal Hydrops, Case of Universal</i> —Pappenheimer.....	147
<i>Field, C. W.</i> —Phenomena of Agglutination.....	35
<i>Flexner, S.</i> —Demonstration of <i>Treponema pallidum</i> .....	207
<i>Flournoy, T.</i> —Case of Diphtheritic Laryngitis, Tracheitis, and Bronchitis .....	213
Case of Generalized Tumor of Lymph Nodes	45
<i>Foot, Angiosarcoma of</i> —Satterlee.....	171
<i>Generalized Tumor of Lymph Nodes</i> —Flournoy.....	45
<i>Gibney, V. P.</i> —Case of Compression Paraplegia.....	102
<i>Gummata, Involution Forms of S. pallida in</i> —Ewing.....	166
<i>Heart, Syphilis of</i> —Janeway and Waite. ....	111
<i>Hypernephroma of Adrenal Gland</i> —Satterlee.....	171
<i>Hypertrophy, Case of Diffuse Bilateral, of Female Beasts</i> — Ward.....	156
<i>Influence of Tissues, Cholesterin and Cholesterin Esters upon</i> <i>Production of Tetanospasmin and Tetanolysin in Fluid</i> <i>Cultures</i> —Noguchi .....	87
<i>Intubation, Rare Sequelæ of</i> —Throne .....	114
<i>Janeway, T. C. and Waite, W. W.</i> —Case of Syphilis of the Heart .....	111
<i>Jobling, J. W.</i> —Metaplasia and Lymphatic Metastasis of a Rat Tumor .....	203
<i>Jones, M. A. D.</i> —Pathological Investigations.....	91
<i>Joseph, D. R.</i> —Ratio between Weight of Heart and Weight Body in Animals .....	205



	PAGE
<i>Laryngitis, Tracheitis and Bronchitis, Diphtheritic</i> —Flournoy	213
<i>Leucocytes, Influence of Injected, upon a Tuberculous Lesion</i> — Opie .....	187
<i>Leucocytes in Protein Absorption</i> —Levene .....	194
<i>Leukemia, Case of Acute Lymphatic</i> —Sabel and Satterlee...	104
<i>Levene, P. A.</i> —Leucocytes in Protein Absorption .....	194
<i>Levin, I.</i> —Case of Endarteritis obliterans .....	213
Reactive Power of White Rat to Tissue Implan- tation .....	180
<i>Le Wald, L. T.</i> —Case of Bilateral Supernumerary Index Finger .....	118
Presence of Amebæ in Mouths of Healthy Individuals .....	119
<i>Libman, E., and Celler, H. L.</i> —Case of Chronic Suppara- tive Lymphadenitis and Pylephlebitis .....	139
<i>Lymphadenitis and Pylephlebitis, Case of Chronic Suppara- tive</i> —Libman and Celler .....	139
<i>Lymph Nodes, Generalized Tumor of</i> —Flournoy .....	45
<i>Lynah, H. L.</i> —Case of Anemia due to <i>Bothriocephalus latus</i>	91
 <i>Malaria, Case of Pernicious</i> —Satterlee .....	171
<i>Metaplasia and Lymphatic Metastasis of a Rat Tumor</i> — Jobling .....	203
<i>Noguchi, H.</i> —On the Influence of Tissues, Cholesterin and Cholesterin Esters upon Production of Tetanospasmin and Tetanolysin .....	87
Sporulation of <i>Bacillus aerogenes capsulatus</i> ..	196
<i>Norris, C.</i> —Case of Acromegalia ....	19
 <i>Opie, E. L.</i> —Influence of Injected Leucocytes upon a Tuber- culous Lesion .....	187
 <i>Pappenheimer, A. M.</i> —Case of Generalized Infection in In- fant with Bacillus of Paratyphoid Group .....	147
Case of Speticemia, Gonococcal in Origin .....	100
Case of Typhoid Fever in Infant...	147
Case of Universal Fetal Hydrops...	147
<i>Paraplegia, Case of Compression</i> —Gibney .....	102
<i>Paratyphoid, Case of Generalized Infection in Infant</i> — Pappenheimer .....	147

	PAGE
<i>Pathological Investigations—Jones</i> .....	91
<i>Phenomena of Agglutination—Field</i> .....	35
<i>Protein Absorption, Leucocytes in—Levene</i> .....	194
<i>Pulmonary Vessels, Case of Arteriosclerosis of—Brooks</i> .....	177
<i>Pyelitis, Double, Ureteritis and Cystitis Cystica—Schultze</i> ..	212
<i>Pylephlebitis, Case of Chronic Suppurative Lymphadenitis</i> <i>and—Libman and Celler</i> .....	139
 <i>Rat, Reactive Power of, to Tissue Implantation—Levin</i> .....	180
<i>Ratio between Weight of Heart and Weight of Body in</i> <i>Animals—Joseph</i> .....	205
 <i>Sabel, S. O., and Satterlee, G. R.—Case of Acute Lymphatic</i> <i>Leukemia</i> .....	104
<i>Satterlee, G. R.—Case of Angiosarcoma of Foot</i> .....	171
<i>Case of Hypernephroma of Adrenal Gland</i> .....	171
<i>Case of Pernicious Malaria</i> .....	171
<i>Satterlee, G. R., and Sabel, S. O.—Case of Acute Lymphatic</i> <i>Leukemia</i> .....	104
<i>Schultze, O. H.—Case of Double Pyelitis, Ureteritis and</i> <i>Cystica Chronica</i> .....	212
<i>Case of Rupture of Cardiac Orifice of</i> <i>Esophagus</i> .....	138
<i>Septicemia, Probably Gonococcal in Origin—Pappenheimer</i> ..	100
<i>Spirillum of Tick Fever, Demonstration of—Terry</i> .....	210
<i>Spirochæte pallida, Demonstration of—Flexner</i> .....	207
<i>Spirochæte pallida, Involution Forms of, in Gummata—</i> <i>Ewing</i> .....	166
<i>Sporulation of B. aerogenes capsulatus—Noguchi</i> .....	196
<i>Stow, B.—Ureteritis Cystica Chronica</i> .....	1
<i>Streptococcus Sepsis, Case of—Bierwirth and Brooks</i> .....	93
<i>Supernumerary Index Finger, Case of Bilateral—Le Wald</i> ..	118
<i>Syphilis of Heart, Case of—Janeway and Waite</i> .....	111
 <i>Terry, B.—Demonstration of Spirillum of Tick Fever</i> .....	210
<i>Tetanospasmin and Tetanolysin, Influence of Tissues, Choles-</i> <i>terin and Cholesterin Esters upon Production of—</i> <i>Noguchi</i> .....	87
<i>Throne, B.—Specimen Showing Rare Sequelæ of Intubation</i> ..	114
<i>Tissue Implantation, Reactive Power of White Rat to—Levin</i> ..	180
<i>Treponema pallidum, Demonstration of—Flexner</i> .....	207



	PAGE
<i>Tuberculosis of Ductus Thoracicus, Case of—Weil</i> .....	211
<i>Tuberculous Lesions, Influence of injected Leucocytes upon—</i> <i>Opie</i> .....	187
<i>Tumor, Metaplasia and Lymphatic Metastasis in a Rat—</i> <i>Jobling</i> .....	203
<i>Typhoid Fever, Case of, in an Infant—Pappenheimer</i> .....	147
 <i>Ureteritis, Case of—Schultze</i> .....	212
<i>Ureteritis Cystica Chronica—Stow</i> .....	1
 <i>Wadsworth, A.—New Desk Bath for Opsonic Work</i> .....	129
<i>Waite, W. W. and Janeway, T. C.—Case of Syphilis of Heart</i>	111
<i>Ward, W.—Case of Diffuse Bilateral Hypertrophy of Female</i> <i>Breasts</i> .....	156
<i>Weight, Ratio between Heart and Body—Joseph</i> .....	205
<i>Weil, R.—Case of Tuberculosis of Ductus Thoracicus</i> .....	211
<i>Wood, F. C.—Decidual Reaction in Ectopic Pregnancy</i> .....	136
 <i>Zinsser, H.—Case of Peritoneal Infection by B. typhosus</i> <i>without Perforation</i> .....	165
<i>Experimental Blastomycotic Lesions</i> ....	121
<i>Mid-Winter Epidemic of Dysentery</i> .....	162





# Proceedings of the New York Pathological Society.

---

NEW SERIES, Vol. VII. FEBRUARY, 1907.

---

No. 1

## TABLE OF CONTENTS

STOW, Ureteritis Cystica Chronica.—NORRIS, A Case of Acromegalia.—FIELD,  
The Phenomena of Agglutination from the Standpoint of Colloidal  
Chemistry.

DR. CHARLES NORRIS, *President.*

## URETERITIS CYSTICA CHRONICA.

(The clinical and autopsy records of a case with bilateral double ureters.)

BOND STOW, A.M., M.D.

The object of this short paper is to bring before you in a cursory review the conclusions reached on this subject by well-known authorities, and particularly to invite your consideration to some recent experimental work by Dr. R. Giani, of Turin, Italy, which throws considerable light on this much debated pathological problem.

The subject is one that has proven solely of pathological interest, although the writer sees no reason why under certain conditions a skilled cystoscopist should not detect this condition during life.

Morgagni,<sup>1</sup> Rayer<sup>2</sup> and Rokitansky<sup>3</sup> were the earliest writers to mention this affection, the latter describing the same in the following clear, concise manner.

"In the mucous membrane of the urinary tract, especially of either ureter, generally in large numbers and groups, there sometimes arise cysts varying in size from that of a grain of wheat to that of a pea, and others of microscopical dimensions. They contain a thin serous or thick colloid, clear or yellowish brown fluid, or gluey resinous clumps."

Virchow<sup>4</sup> maintained that these cysts are true retention cysts the same as the ordinary mucoid cysts of the vagina and are caused by a closure of the crypts of the mucous glands of the bladder and ureter.

Litten<sup>5</sup> was the first to give a careful microscopical study of these cysts and concluded without reservation that the inflammatory catarrh of the mucous membranes of the ureters led to a closure of its crypts and glands, retaining within their lumen their secretions, thus leading to a cystic formation.

Why these cysts occur so rarely in comparison to the great frequency of inflammation and catarrh of these mucous membranes he explains on the ground of the very wide openings of these crypts and the scarcity and uncertain distribution of the glands in these mucous membranes.

R. v. Limbeck<sup>6</sup> as early as 1887, gives an accurate description of this disease and its etiology as judged in the light of Giani's experiments, to be explained later on. He mentions two ways whereby these cysts take their origin:

First, through a union of folds of the proliferating mucous membrane, and second, by a budding process of its epithelium with later a central degeneration and liquefaction of these newly formed epithelial nests and sprouts.

That glands might possibly occur in these mucous

membranes and thus by closure of their exits become a source of these cysts he does not deny, but he states that he with many others has failed to find any such glands.

The English writers Silcock<sup>7</sup>, Eve<sup>8</sup>, Clarke<sup>9</sup>, Bland-Sutton<sup>10</sup>, have accurately described cases of this affection and have drawn particular attention to certain peculiar round or ovoid bodies that are constantly found within the cystic contents, which bodies they interpreted as forms of sporozoa.

Clarke claimed to have found bodies with large nuclei, a well marked network and a nucleolus; conditions only compatible with a perfect state of vitality of cell life. He believed there was an appearance as though the cell was in the process of mitosis although he failed to discover any mitotic figures. He thought it highly improbable that such bodies arose from degenerated epithelium and strongly maintained that they were some variety of protozoa and the direct cause of this disease.

Prof. G. Pisenti<sup>11</sup> describes a case of cystic-pyelonephritis, the right ureter containing numerous irregularly distributed cysts, and the left likewise, though fewer in number. The neck of the bladder also possessed numerous thickly placed small cysts whose contents were a clear fluid. In these various cysts he found the same bodies interpreted by the English writers as protozoa and he coincides with them as regards their etiological importance. He offers no proof that he ever discovered any signs of life in these bodies or that by experiment he was able to reproduce the disease through their agency. His conclusions are simply based upon microscopical observations whereby claiming not to have found within these cysts any transition forms of epithelium, he concludes that these peculiar bodies must be of parasitical and not cellular origin.



V. Kahlden<sup>12</sup> in an exhaustive monograph on this subject also concludes that in his case the histogenesis rests upon a parasitic basis although he does not definitely attempt to classify these supposed parasites, but simply states it as his belief, because of the great similarity between the bodies he found within these cysts and the myxosporidia (a psorosperm found in the bladders of fishes, particularly the pike), that therefore they are either a variety of this class of sporozoa or identical with them. He produces no evidence to support his conclusions from artificial cultivation of these parasites, neither from the reproduction of this disease through their agency by inoculation of lower animals.

One fact opposing the parasitic origin of this disease and prominently claiming our attention is, that no one as yet has found any of these protozoa in or among the epithelial cells of the mucous membrane of the genito-urinary tract or even the cells lining the walls of these cysts. They always appear in the colloidal mass within the cysts. It certainly seems reasonable to expect to find them occasionally (if only by accident) in or among the cellular epithelium when they are present in such large numbers and are supposed to be the causative factor in the formation of these cysts out of the epithelium of the mucous membrane of this tract.

A. v. Brunn's<sup>13</sup> studies on the normal mucous membrane of the genito-urinary tract have proven of great service in elucidating this problem, by showing the existence of certain epithelial bodies found beneath the superficial layer of cells of the mucous membrane, either disconnected therefrom or in direct continuance with the same. He claims that they are in no sense secretory glands as was formerly held by Virchow and Litten, since they fail to show a constant exit duct or central lumen

which is generally present in most glandular structures, and that there are never present within these cells any of those changes frequently observed in glandular organs while functioning. He believes these cellular accumulations are the result of a simple budding process of the normal mucous membrane due to an excessive stimulation and consequent proliferation of the surface epithelium. When these bodies are not disconnected from the surface he speaks of them as epithelial buds or sprouts and the others disconnected by an intervening layer of connective tissue as epithelial cell nests. It is from these cellular formations he maintains that the condition of cystitis and ureteritis cystica chronica arises.

Lubarsch<sup>14</sup> strongly contends against the parasitic origin of these cysts and agrees with v. Brunn, as he has observed all stages of degenerative transition of these epithelial cell nests from solid to complete cystic formations. Clear and forceful is the conclusion to be drawn therefrom, that this is the true origin of these cysts, the two things necessary being the presence of v. Brunn's cell nests and the continuous action of some injurious agent, the most frequent being inflammation arising from the existing calculi. The cysts arise by, first, a destruction of the centrally located cells out of which later is formed a colloid and granular detritus. Since this material finds no exit, by its increment the cyst increases in size until there is but a single layer of epithelial cells that bound the lumen of the ureter. He concludes from microscopical examination and the peculiar action of stains on these cell contents that the same is not a true secretion but simply a colloid mass originating from degenerated epithelium.

Lubarsch by no means thought that this was the sole method of origin of these cysts for at the close of

his article he really speaks of three ways: namely, those cysts that arise from the closure of mucous crypts as described by Virchow and Litten, those that come from a degeneration of v. Brunn's cell nests and those that are found at the trigone of the bladder due to misplaced prostatic glandular tissues.

Aschoff's<sup>15</sup> extensive studies on the mucous membrane of the genito-urinary tract would go to prove that in the newly born and those of early life no epithelial budding of the mucous membrane or cut off epithelial nests as described by v. Brunn and Lubarsch can be found in the genito-urinary tracts and even in adult life he found them to be very inconstant and chiefly confined to the upper third of the ureter.

Marckwald<sup>16</sup> found cystitis and ureteritis cystica in the newly born and claims, as does Aschoff, that an inflammation is not first necessary to originate these cell nests and cysts.

Stoerk<sup>17</sup>, on the other hand, after a most painstaking and exhaustive study of this subject differs from v. Brunn in that he claims these cell buds and nests are secretory in nature as well as their contents and that it is by the retention of their secretions that a transformation of these glandular-like cell nests into cysts occurs.

He also differs from the views of Aschoff and Marckwald in that he strongly maintains that there must be first an inflammatory reaction to cause these cell nests even though traces of such a reaction may have entirely disappeared from present view. He draws attention to one very significant fact that certainly requires explanation, which is, that during extra uterine life nowhere in the body in any of the other mucous membranes can any analogy to v. Brunn's findings be discovered. What explanation can be offered that the



mucous membrane of the genito-urinary tract solely and frequently undergoes this proliferating budding process?

Finally I invite your attention to the most recent work done on this subject by Dr. R. Giani, of Turin, Italy. Giani<sup>18</sup> in a purely accidental way was surprised to find a condition simulating in every respect cystitis and ureteritis cystica chronica caused by some experiments he had instituted for a study of tuberculosis of the genito-urinary tract. He performed a suprapubic cystotomy upon rabbits and placed within the bladder some gelatin capsules containing a pure culture of tubercle bacilli. The external wound and bladder healed regularly. Free passage of urine occurred a few hours after the operation. In one case about 30 days later the capsule was passed through the urethra. In all the other cases the capsules became the seat of salty incrustations from the urine and were the centers of well formed and quite large calculi. The rabbits, twelve in all, were kept alive from fourteen days to three months. After fifteen days he discovered a chronic cystitis and scattered here and there in numerous places the mucous membrane showed marked tendency toward proliferation of its epithelial cells in more or less bud-like processes dipping down into the stratum propium. Later these became wholly separate from the mucous membrane. Still later he found degeneration and liquefaction taking place within their centers and thus the beginning of a small cyst. These epithelial sub-mucous nests varied very materially in size. Sometimes they remained throughout one solid mass of epithelial cells. Complete cystic formation rarely occurred before the 40th day from which time on they increased considerably in size and number. He universally found these cysts, in toto or in part, filled with a fine granular detritus composed of red blood

corpuscles, leucocytes, fragments of nuclei, and broken down epithelial cells. Besides these he frequently found in these cystic contents peculiar bodies whose form were generally round or elliptical averaging in size about 20 to 25 micra though sometimes they were as large as 40 and some were as small as 7 or 8. The protoplasm of these bodies possessed no particular structure. It was more or less coarsely granular and refractory against anilin dyes, having a hyalin, almost glossy appearance, coloring intensely with eosin. Sometimes they contained no nucleus, then again he found a body simulating a nucleus which stained deeply with hematein.

This description corresponds very closely to that of the so called parasites (protozoa) supposed to have been found in the cysts by certain English and Italian writers and claimed by them to be their cause. Such bodies were found only in the cysts and never free in the epithelium of the mucous membrane, neither in the solid cell nests above spoken of and out of which cysts eventually arose, nor in the cell accumulations on the surface of the mucous membrane.

In the light of these experimental findings it is not possible further to give credence to the parasitic origin of this affection. The chronic irritation due to the inflammation set up by the capsules that acted as foreign bodies seems an essential etiological factor.

Giani found the cysts greatest in number where the irritation would appear to have been the greatest.

Further experimentation by ablation of the mucous membrane of the bladder by a Volkmann sharp spoon produced similar results.

Giani also observed in the case of hypertrophy of the prostate where the middle lobe was removed by suprapubic cystotomy that the mucous membrane of the blad-

der over this lobe was covered by numerous epithelial indentations and epithelial nest formations in the submucosa, either isolated or in direct communication with the surface epithelium. These undoubtedly arose from chronic irritation of the mucous membrane of the bladder at this part due both to the hypertrophic middle lobe of the prostate and the daily repeated catheterizations which had taken place for the past three years.

In conclusion one question appears difficult to answer and I cannot help but believe that there is still a very important factor in the etiology of this disease that is yet to be explained.

Ureteritis cystica chronica is a very rare affection.

Lubarsch in over 3000 autopsies met the condition but four times.

The writer's experience which certainly covers many hundreds of autopsies has met with the condition but once; the specimen being presented here to-night (see illustration). I find in the entire literature not over 50 cases reported.

If we are to believe that inflammatory irritations of mucous membrane of the genito-urinary tract set up a proliferation of its epithelial surface so that buds and cell nests are formed out of which later cysts are formed, then why, knowing as we do that inflammation of this tract is of very frequent occurrence, is cystitis and ureteritis cystica chronica so rarely met with? There are several cases reported in the literature of double ureter on one side in which this affection was found.

The specimen presented here to-night is one of bilateral double ureters in which there is complete cystic degeneration of all four ureters. So far as I have been able to glean from the literature it remains the only



specimen of its kind. The cystic degeneration in this case is confined to the ureters. Why?

Is the presence of ureteritis cystica in these cases of reduplication of the ureter purely a concomitant circumstance or has the congenital malformation some etiological significance?

I am not able to answer these seemingly pertinent questions.

Microscopical examination of many sections showed all the finding of the authors above reported especially the round and ovoid bodies in the cyst contents, the budding sprouts and cell nests in the mucous membrane of the ureters with degenerated cell and detritus material in their centers. Nothing was observed that would appear to enhance further the microscopical findings already reported, illustrations of which are plentiful in the literature herewith appended, nor to throw new light on the etiology of this much vexed problem.

### *Clinical History.*

Anna Palil, 40, Hungarian, houseworker. Admitted to Metropolitan Hospital, New York, May 17th, 1906. Died, May 22nd, 1906, 9.25 A.M.

Family history negative. Does not use alcohol. Moderate tea and coffee drinker. No drug habits. Had usual diseases of childhood. Had an attack of articular rheumatism in adult life. No history of any venereal diseases. For the past three years has been complaining of her stomach. Refuses solid food. Says same causes her much distress. No history of any vomiting. No localized pain anywhere in body. Poorly nourished. Subcutaneous and muscular tissues wasted. Edema of both lower extremities. Abdomen presents a large ventral hernia. Face has a pained and distressed

appearance. Complexion is generally sallow with some cyanosis. Mucous membranes congested. No edema of face. Reflexes are all normal. Apex beat in sixth interspace and slightly to the left of the mid-clavicular line. Border of dullness to the right reaches the mid sternal line. Slight epigastric pulsation. A rough systolic murmur is heard at the apex, the same being transmitted to the left axilla. The second pulmonic sound is accentuated. The chest expansion is poor and appears slightly greater on the left side than the right. The apices are somewhat sunken. The interspaces are very much retracted and the ribs correspondingly prominent. Over the entire chest is heard a bronchovesicular respiration except a small area anteriorly on the right side corresponding to about the location of the right middle lobe and the base of the left lung where no respiratory murmur is heard. Large inspiratory moist rales heard over the entire lungs. Expectorates a thick muco-purulent sputum. No tubercle bacilli. Examination of abdominal organs proved negative. Urinalysis showed: light amber color, 1.028 specific gravity, albumin, no sugar, and 1% of urea. Amount was 24 ounces in 24 hours.

*Diagnosis:* Mitral insufficiency with failing compensation, chronic bronchitis and edema of the lungs, chronic Bright's disease.

*Autopsy:* Autopsy began at 2 P.M., 4½ hours after death. Body very pale and anemic. Slight edema of both legs. Abdomen prominent due to gases. Pupils equally dilated 3 m.m. Post-mortem rigor slight, hypostatic congestion in dependent portions of body. No external marks on body. Peritoneum smooth, glistening and transparent. Peritoneal cavity contains about 500 c.c. of a clear pale amber colored fluid. Mesentery and

mesenteric glands show no change. Abdominal organs in normal positions. Diaphragm on right side at lower border of sixth rib and on the left side at seventh interspace. Anterior border of the lungs fully 5 cm. apart. Upper half of right pleural cavity is occluded by old tough fibrous adhesions; lower half filled with a clear pale amber colored fluid amounting to about 800 c.c. Marked thickening of pleura at base of right lung. Left pleural cavity partially occluded by old pleuritic adhesions, and contains about 1000 c.c. of a clear, pale, amber colored fluid. Pericardial sac contains about 200 c.c. of a pale clear amber colored fluid. Pericardium is smooth, glistening and transparent. Right ventricle is soft and collapsible; left is distended. Blood vessels on surface of heart are partially engorged. Heart muscle is of a light yellowish brown color, soft in consistency and readily torn. Left ventricle is distended and its walls measure 7 m.m. at the apex and  $1\frac{1}{2}$  c.m. at the base of the aortic valve. Right ventricle is distended and its walls measure 2 to 3 m.m. Endocardium is smooth, glistening and transparent throughout. Pulmonary and aortic valves show no change. Tricuspid valve is widely dilated. Mitral valve shows recently formed vegetative growths along its free closing margin. The mitral valve is somewhat distended admitting the tips of three fingers. The heart weighs 483 grams. The upper lobe of right lung shows congestion and edema and from the bronchi exudes a creamy, greyish yellow, foamy secretion. The middle lobe is noticeably voluminous, firm to the touch, and its cut surface is of a greyish red color, smooth and glistening and solid and contains no air. The pleura over this lobe is thickened. The lower lobe shows hypostatic congestion and edema with chronic bronchitis.

The pleura covering the upper lobe of the left lung



is covered with numerous recent petechial hemorrhages. The upper lobe shows same as upper right lobe.

The lower lobe is covered by a thickened pleura. It is firm to the touch and upon its cut surface is smooth glistening and airless and of a dull greyish red color.

The larynx, trachea, and upper bronchi were filled with a creamy, foamy, greyish secretion and their walls were heavily congested. Nowhere throughout the lungs was any evidence of tuberculosis. The spleen was of a dark mahogany brown color, capsule slightly thickened, slightly smaller than normal, weighing 180 grams. Cut surface showed trabeculae and Malpighian bodies prominent; pulp firm.

The liver weighed 1447 grams. Firm in consistency with slightly granular surface. Mottled yellowish brown in color. Capsule unchanged. Edges slightly rounded. Cut surface showed same to be finely granular. Acini indistinct. Blood vessels congested.

The pancreas showed no particular change. The stomach walls were covered by a thick, tenacious, slimy mucous. Blood vessels heavily congested. Mucous membrane atrophic, otherwise no change.

The intestines, large and small, showed passive congestion. The adrenals were normal. The bladder contained a foul, stinking, greenish fluid. Its walls were intensely congested. The ureters and pelves of both kidneys likewise contained a foul stinking greenish yellow pus.

There is a reduplication of the ureter on both sides. Each of the four ureters arises from a separate pelvis of the kidney. The two ureters on each side remain entirely separate and distinct throughout (being divided by ordinary connective tissue) and unite in one common

exit at the usual normal ureteral opening at the trigone of the bladder. (See illustration).

Each of the four ureters is very thickly studded from origin to within 4 cm. of its entrance into the bladder by innumerable cysts varying in size from that of a millet seed to that of an ordinary pea.

These cysts are both individual and massed in groups. Some are transparent and contain a clear serous fluid. Others are of an opaque greyish yellow color containing a thick ropy colloid material. A few seem harder than the others and contain a gluey resinous-like hard substance.

The pelves of both kidneys contain likewise a few scattered similar cysts whereas the bladder is entirely free from cysts of any kind. The right kidney is very firm in consistence, of a dark mahogany brown color and weighs  $62\frac{1}{2}$  grams. It measures  $8 \times 5 \times 3$  cm. It is coarsely granular on its external surface and the same is studded with numerous small individual and grouped abscesses.

Its capsule is thickened and cannot be removed without adhering kidney tissue. The cut surface is granular. The cortex ranges from 1 to 3 m.m. The pelves are intensely congested and inflamed. The one pelvis is in direct communication with three large well defined abscess cavities that extend to within 1 m.m. of the external surface of the kidney.

The pyramids are greatly distorted or entirely replaced by tough connective tissue. The blood vessels are prominent and arterio-sclerotic. The left kidney weighed  $93\frac{1}{2}$  grams and measured  $8\frac{1}{2} \times 4 \times 3\frac{1}{2}$  cm. Its color, consistence, and other characteristics are very similar to those of the right kidney. Within the kidney and in direct communication with the pelves of the

kidney are large well defined abscess cavities that contain a foul, stinking, greenish yellow pus.

*Diagnosis:* Chronic bronchitis, passive congestion and edema of the lungs. Unresolved pneumonia of the middle lobe of the right lung. Chronic pleurisy. Hypertrophy and advanced fatty degeneration of the heart muscle with acute endocarditis of the mitral valve. Muscular insufficiency of the mitral and tricuspid valves. Cyanotic induration of the spleen. Early stage of cirrhosis of the liver. Chronic atonic gastritis. Passive congestion of the intestines. Chronic cystitis. Ascending pyelo-nephritis with hydronephrosis and advanced arterio-sclerotic granular nephritis. Complete bilateral reduplication of both ureters. Extensive ureteritis cystica chronica of all four ureters.

Photograph of entire genito-urinary tract.

- A. One of the two left ureters opened throughout and showing the numerous cysts.
- I. Pelvis of the kidney from which ureter A arises. The ureter A can be followed throughout to its common exit (with its fellow B) into the bladder at C.
- B. The other left ureter unopened. The probe at H is passing into this ureter from its own pelvis. The lower end of the probe being seen at C.
- D. Common opening into the bladder of the two ureters on the right side.
- E. and F. The two ureters on the right side opened throughout from the pelvis of the kidney to the bladder. The numerous cysts lining their walls are plainly seen.
- M. The dividing wall of connective tissue between the two right ureters.
- U. Fundus uteri.
- P. Posterior wall of vagina.
- K. Right half of bisected bladder.
- L. Left half of bisected bladder.
- O. O. Ovaries, right and left.
- R. K. Right kidney.
- L. K. Left kidney.





Photograph Showing Entire Genito-urinary System

*Literature.*

1. MORGAGNI.—*De Sedibus et Causis Morborum*, XLII, Art. II.
2. RAYER.—*Traité des Maladies des Reins*, Paris, 1841.
3. ROKITANSKY.—*Lehrbuch der speciellen Path. Anat.* Bd. III, 1861.
4. VIRCHOW.—*Die Krankhaften Geschwülste*, Bd. I, page 246.
5. LITTEN.—*Virchow's Archiv*, Bd. 66.
6. R. V. LIMBECK.—*Zeitschrift f. Heilkunde*, 1887, Bd. 8.
7. SILCOCK.—*Transactions Path. Soc.*, London, Vol. XL, 1889.
8. EVE.—               “               “               “               “               “               “
9. CLARKE —               “               “               “               “               “               “ XLII, 1892
10. BLAND-SUTTON.—*London Lancet*, 1888.
11. PISENTI.—*Central-Blatt f. allg. Path.*, Vol. V.
12. V. KAHLDEN —*Beiträge z. path. Anat. u. allg. Path.*, Bd. XVI.
13. A. V. BRUNN.—*Archiv f. Mikroskop. Anat.*, Bd. 41, 1883.
14. LUBARSCH.—               “               “               “               “               “               “
15. ASCHOFF.—*Virchow's Archiv*, Bd. 138.
16. MARCKWALD.—*Münchener med. Wochenschrift*, 33, 1898.
17. STOERK.—*Beiträge z. Path. Anat. u. Allg. Path.*, Bd. XXVI, 1899.
18. GIANI.—*Central-Blatt f. allg. Path. u. Path. Anat.*, Nos. 5, 22, 1906.

*Discussion.*

DR. CHARLES NORRIS said that he had never before seen a case like this. He would like to ask Dr. Stow whether there were any evidences of tuberculosis found.

DR. STOW said that no evidences of tuberculosis were present throughout the body.

---

## A CASE OF ACROMEGALIA.

CHAS. NORRIS, M.D.

The pituitary tumor in the case of acromegaly which I am about to present is that of a patient, a German by birth, who entered Bellevue Hospital in December, 1902, in the service of Dr. Frank W. Jackson, and who died four years later (Jan. 1907), also in Dr. Jackson's service. I take this opportunity to acknowledge publicly my thanks to Dr. Jackson for his courtesy and kindness in permitting me to report upon the clinical history of the case.

The man was single, a driver by occupation, and, when admitted to the hospital, was 33 years old. He gave the following history:

Six months previously, he was told that his face and hands were growing larger. At this time he began to have dizzy spells. Things became black before his eyes at times. His memory also became poor. His feet became so much larger, according to his statement, that he had to buy larger shoes. At this time he went to St. Francis Hospital, where he remained until two months before admission to Bellevue.

After his discharge from this hospital, he said he was unable to work on account of frequent dizziness, and sharp, radiating headaches. His tongue became enlarged, and impaired his speech somewhat. He became clumsy with his hands, and his gait was a little uncertain. He complained of indefinite pains in his arms. No other important symptoms were elicited, his chief complaint being attacks of dizziness, and severe headaches.

Family and personal history were negative. He had

never been ill before, save for a slight attack of bronchitis nine months previous to admission.

On admission he was fairly well nourished, and rather anemic. Muscles flabby. Poor muscular power. Lips thick. Eyes prominent, lids heavy. Nose large and prominent. Lower jaw projected slightly, although teeth met. Eyes reacted normally to light, and accommodation. Tongue somewhat enlarged, moist and tremulous.

Thyroid gland normal to palpation, and apparently not enlarged. Pulse was rapid, 110.

Heart. Normal, no murmurs.

Lungs. Normal.

Abdominal examination negative.

Hands showed general enlargement, involving bones and soft tissues. Nails were normal. Feet were enlarged, principally the great toes. Reflexes remarkably diminished. Blood examination showed a hypoleucocytosis, 3,400, and rather marked secondary anemia. Hemoglobin 60%. Urine was clear, acid, and contained no albumin, sugar or casts.

From the time of his admission, patient complained of dimness of vision, and severe frontal headaches. Two weeks after admission, ophthalmoscopic examination was made by Dr. Reese, who reported: "Receding choked disc of both eyes. Veins and arteries very tortuous. Nerve margins blurred. Left nerve is atrophic, while right nerve shows beginning atrophy. Pupils react to light directly and consensually".

In January, 1903, without premonition, he was taken suddenly with an epileptic convulsion, lasting five minutes. General muscular spasms, with cyanosis, frothing at the mouth, and dilated pupils. The attack was followed by prolonged stupor. No recollection of



convulsions upon regaining consciousness. Six months later, he had a second convulsion, and from this time until his death, they recurred, gradually, and at decreasing intervals, toward the end, several times a week, and on some days, several convulsive attacks occurred. They were never preceded by definite *aurae*, nor were there at any time localized spasms which might point to a focal lesion. It may be said, however, that the attacks were usually preceded by more intense headache than usual. The headaches, usually frontal, were a persistent and distressing symptom, present the greater part of the time, and but partially relieved by drugs. The visual disturbance was progressive. During the last few months amaurosis was complete in both eyes. On May 19, 1903, in other words, about one year from the onset of the first symptoms, there was noted "neuritic atrophy of the left optic nerve, with no vision. Right eye has 20-20, with + 2.5 diopters spherical. Both nerve heads are filled with cicatricial tissue, margins much blurred. Field in right eye for form is normal, but for red, concentrically contracted".

There was a distinct deterioration of the mental faculties, evidenced by progressive loss of memory for recent events, and by fits of irritability. Other evidence of psychic impairment was never observed.

The nutrition of the patient was well preserved, and the weight remained approximately constant, 194 to 206 pounds. Digestion and appetite were excellent. No attacks of vomiting of the cerebral type were ever present.

Urine. —From his admission in 1902, until May 1905, in other words, for the first three years of his disease, the usual clinical examination showed no abnormalities, save the occasional presence of a few hyaline casts.

From this date, in all subsequent examinations, glucose was present in amounts varying from a trace to 224 grams in 24 hours. The specific gravity ranged from 1.028 to 1.034, averaging about 1.034. Total twenty-four hour amount never exceeded four litres. No examination for acetone or diacetic acid is recorded. For a time in the Fall of 1903, and the Spring of 1904, the patient received Parke Davis's pituitary extract, without obvious benefit, although the patient said that he felt better.

During life, the patient had a marked stooping carriage. Death occurred on January 19. Patient had had a series of severe convulsions, followed by a coma and Cheyne-Stokes respiration.

Summary of Clinical History.—Total duration of illness, June, 1902, to January, 1907, —  $4\frac{1}{2}$  years.

Principal Symptoms: Progressive enlargement of jaw, nose, ears, hands and feet. Persistent frontal headaches, and attacks of vertigo. Gradually increasing loss of vision, ending in double optic nerve atrophy and practically complete blindness. Recurrent epileptiform attacks. Glycosuria for twenty-two months.

For the present purpose, only the significant features of the post-mortem findings need be given.

The body was that of a large, well-developed and well-nourished male, about 90.9 kilos in weight. Length of body on table, 5 ft.  $8\frac{1}{4}$  inches.

The general appearance of the face was not as striking as it was during life; the lower jaw did not appear as large and prominent. The nose, however, was large and long. Lips were somewhat thickened. Teeth and gums were normal. The ears were markedly hypertrophied and symmetrical. This difference in appearance at autopsy was due, it seems to me, to the characteristic posture of the patient during life, his lower

jaw thrown forward, his head lowered, and marked stooping carriage. In other words, the kyphosis that was so prominent a feature in life was a physiological one, since the vertebral column at autopsy was found perfectly straight. Although the forehead was receding, the supraorbital ridges were only slightly prominent. The skull was brachiocephalic,  $22\frac{1}{2}$  inches, "sub-occipito-bregmatic". The eyes protruded markedly, even at autopsy. Chest was long and broad, the lower opening being especially wide. The sternum was not enlarged. The costal cartilages were broad, the fourth left, in its broadest portion, being 25 mm., in its narrowest, 20 mm. The ribs, although at autopsy they appeared to be broad and heavy, may be said to be only slightly larger than normal, corresponding in size to those of a man of the patient's size.

Circumference of chest,  $38\frac{3}{4}$  inches. From tip to tip of acromion process, 18 inches. Glove measurement,  $8\frac{1}{2}$  inches. Across fingers, 8 inches. Middle finger,  $4\frac{1}{2}$  inches long. Foot measurement around metacarpal joint,  $9\frac{1}{2}$  inches. Circumference of big toe, 4 inches. From these measurements, it can be readily seen that the feet and hands were not greatly enlarged. Neither were the subcutaneous tissue and skin hypertrophied. Enlargement of both big toes, however, was a striking feature. No osteophytes were felt.

The small toes were likewise greatly enlarged. The fingers were large and sausage shaped. The nails were broad, but otherwise normal. The subcutaneous tissues of the toes and fingers were hypertrophied. The corium taken from the abdominal wall was hypertrophied.

To be brief, it may be said that the viscera were practically normal, with the exceptions to be noted. Considering the size of the body, it may be safely

asserted that the so-called condition of splanchnomegalia was not present.

Heart. Normal. Weighed 473 grams — normal to the body weight.

Liver. Weighed 2,930 grams, being slightly below weight in proportion to that of the body.

Spleen. Weighed 510 grams, being almost double in weight. The capsule was wrinkled.

Kidneys. Together weighed 360 grams. Normal relation to body weight.

Pancreas. Length 20 cm.; large; weighed 170 grams, in relation to the body weight  $\frac{1}{6}$  above normal. The organ was firm, the lobulations being distinct. No macroscopic lesions were noted. The organ underwent rapid post-mortem softening.

Thymus was persistent, and extended to the auriculoventricular junction below, and to the thyroid gland above. The left lobe was somewhat larger than the right, and very broad. Weight of gland was 70 grams.

Tongue. Was very large and broad, measuring from apex of tongue to apex of circumvallate papillae, 11 cm. Maximum breadth, 7 cm. The papillae were extremely large.

Lingual tonsils were large. In the pyriform fossae of the larynx, on the anterior surface of the epiglottis, numerous small, raised, grayish bodies, averaging 4 to 5 mm. in diameter, were present.

Thyroid. Thyroid cartilages showed reddish bone-marrow. Thyroid gland was symmetrical, normal in size and appearance. The cervical lymph nodes were somewhat increased in size, and slightly yellowish in color. The lymph nodes of other regions were normal in size. The only lymphatic hyperplasia that was noted was



found in the larynx and pharynx, the splenic follicles of the spleen not being hyperplastic.

**Gastrointestinal Tract.** Stomach, moderate *état mamelonné* in pyloric region. Otherwise the gastrointestinal tract was normal.

The genitourinary tract was normal, the penis and testicles being well developed.

The Cranium may be said to have been normal to the size of the body. The bones of the face, with the exception of the inferior maxillae, were not enlarged. The scalp tissues were normal. On stripping the scalp from the calvarium, the parietal bones were found markedly hyperemic. Bones of the skull were soft, being readily sawn. The temporal bones were thin, only 2 to 3 mm. in thickness.

Over the right frontal base, the bone measured 9.5 mm. Here the diploe was extremely hyperemic, 4 mm. in thickness. Outer table measures 3 mm, inner table 2 mm. Dura presents over both cerebral convexities, a number of flat, whitish chalky plaques, the largest 5 to 6 mm. in length. The pia shows no opacities. The cerebral convolutions over the convexities are markedly flattened, the sulci being almost obliterated.

On lifting the frontal lobes, a tumor mass was found on the inferior surface of the right frontal lobe. Owing to the apparent attachment of the tumor to the pituitary gland, the brain was removed with sella turcica, and adjacent parts of the base of the brain. The tumor mass need not be described, except to mention the measurements. The tumor mass seen in the frontal lobe measured 5 cm. in length antero-posteriorly, 4.5 cm. in breadth, and approximately 3 cm. depth. It was dull grayish, approximating brain tissue in color and consistency. On section it had a fleshy appearance, and was in places hemorrhagic.

The tumor mass was connected by a broad pedicle to the pituitary gland proper, which was enlarged, being represented by a spheroidal mass of tissue, roughly speaking, 30 mm. in diameter. The bone of the sella turcica was very thin and fragile, and was readily separated from the pituitary gland tumor proper, with forceps. The adjacent sphenoid cells were likewise distinctly atrophied, and filled with a semigelatinous fluid.

The pituitary tumor, in its growth, has enlarged the sella turcica, and pushed aside the sphenoid cells and the clinoid processes. The tumor has advanced upward and forward, pushed aside the right olfactory lobe in front of it, and has gradually developed into the large tumor which was found at autopsy. In its growth, it has invaginated the R. lateral ventricle, especially its anterior horn, the ventricle being converted into a narrow slit, and the corpus striatum, with the internal capsule, compressed into a narrow band, which, in its widest portion, is approximately 1 cm. in breadth. The sections and photographs show the distention of the left lateral ventricle.

The brain with the pia mater was above the normal weight, 1,678 grams. The medulla and spinal cord were broad and large. There are two calcareous plaques, similar to those found in the dura mater of the cerebrum, in the spinal pia mater.

**Osseous System.**—The marrow of the ribs is extremely scanty. Marrow of one of the lumbar vertebræ may be said to be normal in appearance. Marrow of the lower end of the femur was, to the best of my recollection, normal in appearance.

In review, the main features of the necropsy are the following:

Enlargement of the inferior maxillæ, of the nose

and the ears, characteristic of those found in acromegaly. Likewise enlargement of the fingers and toes, especially the great toes. The presence of a large pituitary tumor. Hypertrophied tongue. Hyperplasia of the lingual and pharyngeal lymphadenoid tissue. Persistent thymus. Large pancreas. Large spleen. Hypertrophy of the corium of the abdominal wall.

Microscopic Examination.—Examinations of the sections from the liver, spleen, heart, kidneys, suprarenals, small and large intestines, show no noteworthy features.

Testicles. — Show active spermatogenesis.

Thyroid Gland.—Sections of the thyroid gland; the alveoli present the normal variations in size invariably observed in all normal thyroids. No colloid vesicles were noted in the sections or in the gross.

Sections taken from various parts of the tumor resemble closely the normal histological structure of the pre-hypophysis. The tumor is made up of a mass of spheroidal or oval cells, which are grouped in irregularly-shaped lobules or alveoli, by delicate capillary walls, apparently composed only of endothelial lining. At the periphery of the lobules, the cells appear to lie directly upon the endothelial lining of the capillaries. In sections stained by Van Gieson's stain, dilated connective tissue fibrils are, however, made out, separating the cells from the capillary wall. The tumor is everywhere very vascular, and in a few places small areas of hemorrhagic infiltration are present. The lobules are in the main closely packed with cuboidal cells. The nuclei are small, usually oval. The chromatin network is scanty, nuclear membrane is distinct. The protoplasm is moderately eosinophilic, and the cell boundaries indistinct. The

stroma, as above said, is scanty. Nowhere in the tumor have whorls of connective tissue been seen.

The two types of cells described in the normal prehypophysis cannot be made out, or their presence is only in a few places suggested. It is, however, quite true that there are variations in the staining reactions of the cells, but these are insignificant, in some places the protoplasm being more eosinophilic than in others. In some places, the protoplasm of the cells appears more granular and the lumina of the acini contain globules of various sizes, as well as a smaller number of free cells, some of which are well preserved, while others have poorly staining nuclei. In many sections there are seen groups of larger and smaller acini, lined with a single layer of high columnar epithelium, the cells of which are closely packed together. The nuclei of these cells are oval, and have a scanty chromatin network and small nucleoli. The protoplasm of these cells is granular and moderately eosinophilic. In their lumina, is found more or less granular material, and globules staining with eosin. These globules invariably stain less intensely than the red blood cells.

The most striking feature of the tumor may be said to be its extremely cellular and vascular structure. The abundance of the material and globules present in the lumina of the acini is a most noteworthy feature, and in this respect, the tumor may be said to vary from the normal anterior lobe of the pituitary gland.

The histological descriptions of the adenomatous tumors of the pituitary gland in cases of acromegaly, do not mention such a condition, as far as I recollect, but I am not yet sufficiently familiar with the literature of the numerous articles to be sure of my ground. Frozen sections stained with Scharlach Roth present a few fat droplets, much less than in the normal gland.



Thymus.—Microscopically, shows the structure usually found in the organ which persists during adult life.

Pancreas.—Except for the changes to be described in the islands of Langerhans, is normal. There is no interlobular or interacinal pancreatitis. There are small areas of post-mortem degeneration, which present the usual features: that is, the nuclei stain poorly or not at all, and the tissue takes with hematoxylin a diffuse bluish tint. The vessels in places show slight thickening. The islands in the sections taken from the middle regions of the organ, show the following changes: The cells of many of the islands are hyperplastic, and here vascularity of the capillaries is a noteworthy feature. The cells frequently take on a rather intense eosinophilic stain. In a few islands, the changes noted by Opie are marked; that is, the islands are composed mainly of an indefinite substance, which has undergone hyaline degeneration. The lesion of the islands may be considered as an early stage of the condition which Opie has described in the pancreas of cases of diabetes mellitus.

On account of the lack of time at our disposal, it will be impossible to give a description of the lesions and various theories which have been formulated upon the etiology of acromegalia. Since Sternberg's elaborate article in Nothnagel's System, which appeared in 1897, little advance may be said to have been made in our knowledge of this disease.

Sternberg reviewed 210 cases. Since that time, numerous other cases have been reported. Tamburini, in 1897, reported upon 30 cases with autopsies. He noted that all had tumors of the pituitary—either a simple hypertrophy of the gland, or a total involvement in an adenoma, in which were preserved the principal elements of the gland. Tamburini was the first to bring out the

theory of hypersecretion as the etiological factor of the disease. He based his view on the following facts:

In acromegalia, the gland was never atrophied, and the symptoms of the disease were absent in cases of pituitary tumors which are heterological or atypical of the normal pre-hypophysis, in other words, where the gland was atrophied or diseased, or in a condition where it was reasonable to suppose that abolition of its function has occurred, the disease was not present. He therefore concluded that the constant presence of a tumor, and the nature of these tumors—hypertrophy or typical adenoma—supported the view that acromegalia is caused by a hypersecretion of the gland. The disease process is thus analogous to that of Basedow's disease.

In an elaborate and complete article which appeared in 1898, in which three cases, with autopsies, were reported, Brooks has supported Tamburini's hypersecretion theory.

Sternberg has divided cases of acromegalia into three groups, according to the duration of the disease. (1) The benign form, the disease running a slow course (50 years) with slight symptoms. (2) The usual form, 10 to 20 years. The majority of cases fall in this group. (3) The acute malignant form, 3 to 4 years. The cases now reported would fall in this group.

Six cases were reported by Sternberg, as belonging to the acute group. One of these was by Hansemann. In all the cases running an acute course, and only in these, was there observed a true sarcoma of the gland. These are of great interest in connection with the etiological relationship of a hypersecretion of the gland to the disease process. For, in a true sarcoma of any organ, one would not expect to find hypersecretion. Brooks, in order to overcome this difficulty, has boldly asserted that

the cases reported as sarcoma were not correctly diagnosed, claiming that they were probably all of them adenoma or hyperplasia. It seems almost impossible to believe that this view can be correct, for it is reasonable to suppose that such an observer as Hanseemann would be familiar with the normal structure of the pituitary gland.

In the case now reported, the resemblance of the tumor of the normal gland is so very striking that I believe no one could fail to identify it as the pituitary gland.

The point I wish to emphasize especially this evening, is my firm conviction that in doubtful cases of acromegalia, the so-called *formes frustes*, that is, those cases in which the upper jaw is large, the lower being small, the face presenting the *type carré*, as opposed to the *type ovoïde*, the diagnosis of the disease cannot be made from the histological appearance for the following reasons: First, because it is extremely difficult to be certain of the existence of hypertrophy in any gland, especially so in the case of the pituitary gland, and, second, because the presence of a small adenoma is not an unusual occurrence where no acromegalia is present. Erdheim thus reports a case of a man 42 years old, with an adenoma, the gland being normal in size. We have the same condition of affairs in connection with the thyroid, for it is undoubtedly true that many cases of parenchymatous struma are not accompanied by Basedow's disease.

In many cases of acromegalia, the gland has been found normal in size, and special emphasis seems to have been made upon the soft condition of the organ, a not unusual characteristic in cases dying with high fever, in meningitis, etc., where the post-mortem changes may be rapid, and also where care is not exercised in removing the gland from its bony surroundings.

Special attention has been called to the increased number of chromophile cells in the pituitary tumor of acromegalia. These cells are considered to be the functioning cells of the gland, and this fact has lent support to the hypersecretion theory. In our case, the chromophile cells are not increased in number, and, in fact, none of the cells can be said to resemble the chromophile cells which are found in normal glands, a statement in accord with Erdheim's description of the histological structure of the pituitary tumor in the case of acromegalia he reported.

Before closing, it may be of interest to state briefly that gigantism is frequently associated with acromegalia. According to Sternberg, 20% of the acromegalics are over 177 cm. in height, that is, 5 ft. 11 in., and 40% of all giants are acromegalics. It is thus seen that all giants are more often acromegalics than acromegalics are giants. According to Kundrat, giants are subject to all sorts of dystrophies and vegetative disturbances, and therefore, they are predisposed to become acromegalics.

The association of glycosuria with acromegalia is a very constant one. The physiological relation of the gland to the pancreas, has, as far as my knowledge extends, not been definitely settled. That the relationship between the pituitary and the thyroid gland is a close one, is well known. A persistent thymus has been noted in a large number of cases.

Two views are held concerning the two types of cells found in the gland. (1) Saint Rémy (1892) suggested that the two types of cells were merely functional stages of one cell. Benda (1900) was apparently able to trace the transition from the chromophobe or chief cell to the eosinophilic or chromophile cell. The small cells, with few granules, according to him, are the indefinite em-



bryonal cells which are multiplying, the large granular cells being actively functioning.

Scaffidi (1904) held the opposite view, namely, that the two types of cells have different functions, each type of cell producing a specific substance, a view apparently confirmed by the experimental results obtained by Schäfer and Vincent (1899) who extracted two substances from the gland, one depressing, the other stimulating the nervous system, and raising the blood pressure.

BENDA.—*Berl. klin. Wochenschrift*, 1900, XXXVII, pp. 1205-1210.

BROOKS, HARLOW.—*Acromegalia. Archives of Neur. and Psychopath*, 1898, I. p. 485.

ERDHEIM.—*Beiträge zur path. Anat. und allge. Pathol.*, 1903, Bd. 33, p. 227.

SAINT RÉMY.—*Arch. de Biologie*, 1892, XII, pp. 425.

SCAFFIDI.—*Arch. für mikr. Anat., Bonn*, 1904, LXIV, p. 235.

SCHÄFER AND VINCENT.—*Journ. Physiol*, 1899, XVI, p. 87.

STERNBERG.—*Nothnagel's System*, 1897.

TAMBURINI.—*Archiv. de Neurologie* 1897, Tome V. p. 621.

### *Discussion.*

Dr. J. H. LARKIN asked Dr. Norris whether he had made any observations on the condition of the bone in connection with the sella turcica. The tumor might have arisen from the stalk of the gland and not from the gland primarily. This would bring out a very interesting condition of affairs, and it would be interesting to know whether the bone in connection with the gland was necrotic or had been eroded.

Dr. HARLOW BROOKS said that since Dr. Norris had been kind enough to refer to his paper he would like

to say a few words in defense of his attitude. In addition to the three cases which he had reported he had had three other autopsies since. In all of these he had found conditions identical with his first three cases. All of them were younger cases. One of the original cases reported he had considered as of great value because the patient had died of a concurrent infection in the early stage of the disease. In this case an adenoma of the hypophysis had been found in which the new formed cells were entirely of the chromophilic type. Dr. Brooks had then advanced the theory that the condition was due to a hypersecretion of the gland elaborated by the acidophilic cells alone. In regard to his position as to what he considered the faulty diagnosis of sarcoma by Hansemann, Virchow, and others, Dr. Brooks said that in none of these cases were there any metastases. In most of the cases the duration was not less than ten years, in all from four to ten years. Did it not seem rather strange that we could have here a sarcoma situated in such an advantageous position, running for ten years without a single metastasis? He thought a careful analysis of these cases would lead one to see that he had not been so far wrong in thinking that a mistake might have been made in diagnosis. Another thing which seemed to him of importance in regard to the sarcoma theory was that in none of the cases had there been any actual infiltration of the tissues from the tumor growth. In the cases described, while the sella turcica had undergone necrosis, in none were the tumor cells described as infiltrating the bone. Dr. Brooks still thought that no sarcoma had been proved to be present in a case of acromegalia. Of course, sarcoma of the hypophysis had been described, but it would be recalled that it was very hard to get a sarcoma of the hypophysis. If there is a sarcoma it

must arise from the mesodermal elements which are infrequent in the prehypophysis and which usually simulate the normal cells of the epiderm or at least of the entodermal cells. Dr. Brooks had seen one case which had somewhat shaken his theory. This was a case of adenoma of the hypophysis of sufficient size to make a diagnosis possible. The cells in this case were of the same variety before mentioned, but nevertheless acromegalia could not be demonstrated. This had shaken his theory more than anything else.

Dr. Norris said, in regard to Dr. Larkin's question, that in endeavoring to make his paper as short as possible he had omitted some points. The brain had been removed with the sella turcica and adjacent bones. The sella turcica was converted into a delicate shell of bone. He was sorry that he had given a wrong impression in speaking of the cases described as sarcoma; in fact, he was inclined to think that Dr. Brooks was perhaps right in saying that a mistake in diagnosis had been made, though it was hardly possible to conceive that such observers could make a diagnosis and not know what a normal gland looked like. In his own case he thought that it would be impossible to make a mistake in diagnosis.

## THE PHENOMENA OF AGGLUTINATION FROM THE STANDPOINT OF COL- LOIDAL CHEMISTRY.

CYRUS W. FIELD, M.D.

I wish to bring to your attention this evening the result of some work which has been going forward for the last six or seven years in colloidal chemistry, especi-

ally as this work bears on the phenomena of agglutination and precipitin reactions.

Linder and Picton, in England, determined the coagulative effect of various salts on colloidal arsenic sulphide, and found that this power was a function of the metallic cation and varied directly as its valence. (That is, if one part of a monovalent ion will flock out of solution one part of a colloid, one part of a divalent ion will flock out 35 parts of colloid, and one part of a trivalent ion will flock out 1,023 parts of colloid. This, as you will see, is in the ratio of  $1:x:x^2$ , or in geometrical progression. If we represent  $x$  by an arbitrary number, 32, we then have  $1:32:1,024$ . This is in very close agreement with the figures obtained by actual experiment.)

Hardy, working with coagulated egg albumin, found the same phenomena and explained it on the same basis. Billitzer and Bechhold have both worked on this subject with various colloids and also with suspensions, such as lamp black and bacteria. They found the same action; that is, they found that these colloids and suspensions were flocked out of solution by the electrolytes.

Buxton, Shaffer and Teague published a paper last summer in which they demonstrated two things; first, that it required less electrolyte to flock out bacteria which had been saturated with their specific agglutinin; second, that bacteria to which an insufficient amount of electrolyte to cause flocking out had been added, still traveled to the anode, and that when more than enough electrolyte than was sufficient to cause flocking was added, there was a reversal of the sign of the bacteria; that is, they traveled to the cathode.

When dialyzed bacteria are brought into the presence of their dialyzed specific agglutinins they ab-



sorb the agglutinin, but the organisms are not flocked out. If they are washed with distilled water and thus separated from all traces of their serum, and then suspended in distilled water, we have a preparation to which we apply the term agglutinin bacteria.

Table I shows the irregular series of agglutination; for instance, the colloidal platinum is flocked out at 2 normal to a 1-20 normal concentration of the salt. From 1-50 normal to a 1-1000 normal, no agglutination takes place; but at a 1-1500 normal to a 1-4000 normal we again have agglutination.

The dialyzed typhoid bacilli are flocked out from 1-10 normal to a 1-1000 normal. In this series we see a very pretty prozone; that is, no flocking has taken place in concentrations above a 1-10 normal. But in the case of the agglutinin bacilli, there are traces of agglutination from a 2 normal to a 1-20 normal, and complete agglutination at a 1-50 normal; then we have no agglutination taking place until we reach the 1-4000 normal and 1-6000 normal concentrations. Here we have a prozone from a 1-200 normal to a 1-2000 normal concentration of the salt.

The theory in regard to this is that all colloids carry an electric charge. For instance, bacteria are electronegative. Colloidal silver, gold, platinum, etc., are also electronegative. Aluminium hydroxid, ferric hydrate, and a number of other colloids are positively charged. Now, Bredig has shown that the surface tension of mercury when in contact with an electrolytic solution is greatest when the potential is least; in other words, when the electric charge is decreased, the surface tension is increased. We see, therefore, that when the charge of these particles is lowered the surface tension is increased and they must in some way overcome this tension. To

TABLE I.  
Abstracted from BUXTON and TEAGUE.

Concentration of $\text{Fe}_2\text{Cl}_6$	Colloidal Platinum	Typhoid Bacilli	Agglutinin Typhoid Bacilli
2 Normal	-- + +	0	Trace
1 Normal	-- + +	0	Trace
1-2 Normal	-- + --	0	Trace
1-4 Normal	-- + +	0	Trace
1-10 Normal	+ + +	+	Trace
1-20 Normal	+ + +	+ +	Trace
1-50 Normal	0	+ + +	+ + +
1-100 Normal	0	+ + +	Trace
1-200 Normal	0	+ + +	0
1-400 Normal	0	+ + +	0
1-600 Normal	0	+ + +	0
1-1000 Normal	0	+ +	0
1-1500 Normal	+ + +	0	0
1-2000 Normal	+ + +	0	0
1-4000 Normal	+ + +	0	+ + +
1-6000 Normal	0	0	+ + +
1-8000 Normal	0	0	Trace
1-16000 Normal	0	0	0

do this they unite to form a less number of particles of larger size, because the total surface of two equal spheres is more than that of one sphere of double the mass of one of the smaller spheres. It is believed that these negatively charged colloids adsorb the positively charged metallic ions and in this way their charge is lowered and their surface tension is increased.

If this be true, the colloid particles should travel more slowly; that is, if they coalesce and form particles of a larger size, it should take a greater current to move them.

This point has been worked out by Burton, under J. J. Thompson in the Cavendish Laboratory. He used colloidal gold and silver, and flocked them with aluminium sulphate.

TABLE II.  
Abstracted from BURTON.

Grams of Al	Specific Conductivity	Pole to which particles traveled	Velocity cm. per sec.	Precipitation
Silver Solution				
0	$31. \times 10^{-6}$	+	$22.4 \times 10^{-5}$	0
$14. \times 10^{-6}$	$30.3 \times 10^{-6}$	+	$7.2 \times 10^{-5}$	Trace
$30. \times 10^{-6}$	$29.7 \times 10^{-6}$	—	$5.9 \times 10^{-5}$	Trace
$77. \times 10^{-6}$	$28.5 \times 10^{-6}$	—	$13.8 \times 10^{-5}$	0
Gold Solution				
0	$3.6 \times 10^{-6}$	.	$33 \times 10^{-5}$	0
$19. \times 10^{-6}$	$5.2 \times 10^{-6}$	+	$17.4 \times 10^{-5}$	Trace
$38. \times 10^{-6}$	$6.6 \times 10^{-6}$	—	$1.7 \times 10^{-5}$	Trace
$63. \times 10^{-6}$	$11.6 \times 10^{-6}$	—	$13.5 \times 10^{-5}$	0

In Table II it is seen that the colloidal silver travels to the anode at a velocity of  $22.4 \times 10^{-5}$  when no aluminium is present; but when 0.000014 grams of this cation are added, the particles move at a velocity of  $7.2 \times 10^{-5}$ , or only one-third of the original rate. When 0.00003 grams of aluminium are added, the direction in which they travel is changed; that is, they now pass to the cathode; and the velocity is  $5.9 \times 10^{-5}$ .

The column under precipitation shows at what points they are agglutinated. I need not discuss in this place the significance of the other figures.

Table III shows the rate at which typhoid bacilli travel after having been treated with varying amounts of  $\text{Fe}_2\text{Cl}_6$ .

As will be noted, when no salt was present they wandered 2 cm. toward the anode in 60 minutes; but when they had been treated with a 1-6000 normal  $\text{Fe}_2\text{Cl}_6$  solution, they required 110 minutes to travel 2 cm. in the same direction. When a 1-100 normal solution was added, they did not travel at all as they were completely agglutinated. If a 1 normal solution was added they moved to the cathode 2 cm. in 150 minutes; and when a 5 normal solution was added they traveled the 2 cm. in 115 minutes.

TABLE III.

Concentration of $\text{Fe}_2\text{Cl}_6$	Sign of Charge	Wandered 2 cm, in	Agglutination
0	—	60 min.	0
1-6000 Normal	—	110 min.	0
1-100 Normal	?	$\infty$	+ + +
1 Normal	+	150 min.	Trace
5 Normal	+	115 min.	Trace



As is seen the sign is changed when they are treated with either a 1 normal or a 5 normal  $\text{Fe}_2\text{Cl}_6$  solution.

It has been shown that bacteria when heated give up their agglutinins. That this same thing occurs with electrolytes that have been adsorbed is shown by the increased conductivity after heating to  $50^\circ \text{C}$ . for 1 hour, as may be seen in Table IV.

TABLE IV.

10 c.c. typhoid bacilli—40 c.c. of 1-80 normal  $\text{CuCl}_2$  sol.  $18^\circ \text{C}$ .

Treatment	Ohms	Mohs
The above 50 c.c. at once .....	16,667	$57.2 \times 10^{-6}$
The above 50 c.c. 24 hrs. later .....	14,667	$68. \times 10^{-6}$
Bacteria thrown down by centrifuge and A. & B. tested A 15 c.c. of sediment—28.5 c.c. of $\text{H}_2\text{O}$ .....	122,223	$8.18 \times 10^{-6}$
B 2 c.c. of supernatant fluid—28 c.c. $\text{H}_2\text{O}$ .....	220,000	$4.5 \times 10^{-6}$
A heated to $50^\circ \text{C}$ . for 1 hr. ....	84,614	$10.5 \times 10^{-6}$
B heated to $50^\circ \text{C}$ . for 1 hr. ....	220,000	$4.5 \times 10^{-6}$
A centrifuged and sediment dil. with 15 c.c. $\text{H}_2\text{O}$ .....	366,667	$2.7 \times 10^{-6}$
Heated to $50^\circ \text{C}$ . for 1 hr. ....	275,000	$3.6 \times 10^{-6}$

There is a point which this theory explains, in regard to agglutination, and that is the prozone. For we believe that in this zone the charge of bacteria or colloidal particles has passed the isoelectric point, and that they are now charged with the opposite sign; therefore, the surface tension is reduced sufficiently to permit them to remain in suspension or in colloidal solution. This explanation seems to me to be much more rational than that advanced by Eisenberg who following Ehrlich's hypothesis explains this by suggesting that there is a substance in the serum which has a greater affinity for

the bacteria than the agglutinins; but that this has no agglutinating action; and that in this way this substance blocks the receptors of the bacilli and so prevents them from uniting with the agglutinins.

This same theory (the neutralization of the electric charge) has a bearing on immunity. For instance, Noguchi has shown that if an acid is added to a complementary serum the complementary action is destroyed; on the addition of an alkali the action reappears when the neutral point is reached, but again disappears on the addition of more alkali. The explanation appears very simple when we know that the surface tension between the colloidal particles and the serum is increased on the addition of acid and the size of the particles is increased. Owing to this enlargement the complement is bound by these larger colloidal particles and so can not act; but on the addition of an alkali the surface tension is decreased and the particles again separate and the complement is set free. When serum is heated to  $55^{\circ}$  C., the size of the particles begins to increase, and when the serum stands for a time the state of aggregation of the colloidal particles increases. In view of this it seems to me that inactivation of complement is a physical phenomena and not a chemical action, that is, it is entangled in the larger colloidal aggregate.

The question now arises, how do colloids of the same sign act? Agglutinins carry a positive charge and bacteria a negative charge; and it is easy to understand this phenomena. But toxins and antitoxins are both positively charged colloids. Personally I have no doubt that two colloids of the same sign can unite. I have recently prepared an extremely pure ricin and by immunizing rabbits to this have got an antiricin. The ricin is positively charged, and tests of the antiricin produced in

these rabbits have shown that it also is a positively charged colloid. I do not think that the two colloids unite chemically, but that they do adsorb one another and perhaps ultimately a solid solution is formed. I am working on this point and hope to be able to determine something in regard to it soon.

---



# Proceedings of the New York Pathological Society.

---

NEW SERIES, Vol. VII.

MARCH, 1907.

No. 2

---

## TABLE OF CONTENTS

FLOURNOY, An Unusual Case of Generalized Tumor of the Lymph Nodes.—  
BREWER, A Case of Blastomycosis.—BROOKS, An Experimental Study of  
Caisson Disease.—NOGUCHI, On the Influence of Tissues, Cholesterin and  
Cholesterin Esters upon the Production of Tetanospasmin and Tetanolysin  
in Fluid Cultures.—JONES, Pathological Investigations.—LYNAH, A Case  
of Anemia due to *Bothriocephalus latus*.

---

DR. CHARLES NORRIS, *President*.

---

## AN UNUSUAL CASE OF GENERALIZED TUMOR OF THE LYMPH NODES.

THOMAS FLOURNOY, M.D.

The autopsy on this subject and a large part of the subsequent work were done by Dr. Norris, to whom I am indebted for permission to present the case.

The clinical history is somewhat meager, the patient being a German who spoke and understood little English and was almost aphonic on account of certain throat conditions. He entered the service of Dr. Bryant of Bellevue Hospital, December 31, 1906. Dr. Bryant has very kindly given us permission to present the clinical history.

The patient was a male, forty-five years of age.



The family and previous personal history were negative. For fifteen years he had been employed in a grocery store. About two years ago, while in Harlem Hospital on account of a broken arm, there were removed from the right side of his neck several enlarged glands which he had first noticed about three months previously. Subsequent to this operation the remaining glands in the neck became enlarged, as did also the inguinal lymph nodes, though these latter in time again became small.

Three months after operation he became hoarse and had difficulty in swallowing. These symptoms increased gradually, but with periods of improvement.

About a year ago he entered City Hospital because of dyspnea. His legs at that time were swollen, and the glands in the neck were large and were considered inoperable. A tracheotomy was performed, evidently to relieve his dyspnea.

Little reliance can be placed on the clinical history for the reason that when his history was taken by another person he admitted that he had had enlarged glands in the neck for five years and said that he had been operated upon at the Presbyterian Hospital. Unfortunately there are no records of his admission either at the Harlem or Presbyterian Hospitals.

His chief complaint, when in the hospital, was weakness, dyspnea and swelling of the legs. There were present two scars, one from a curved surgical incision on the right side of the neck, and another in the median line as a result of the tracheotomy incision. Large, firm, nodular masses extended from the ear to the clavicle on the right side of the neck, and similar masses, smaller in size, were present on the opposite side of the neck. The right axilla was occupied by a large mass of nodes. In the opposite axilla, the nodes were smaller, but palpable. A

small subcutaneous nodule was present near the right nipple.

Enlarged glands were present in both Scarpa's triangles. Those on the right side were larger. The liver extended below the arch of the ribs, and the area of splenic dullness was large. The upper half of the abdomen was distended by an indefinite tumor mass. The left elbow was partially ankylosed, and the muscles of the upper and lower arms were atrophied from disuse. The left leg was edematous.

The urine was negative. Blood examinations revealed nothing noteworthy.

A provisional diagnosis of alveolar sarcoma was made from a specimen removed from the neck. The subcutaneous nodule near the right nipple was removed, and on examination the diagnosis of endothelioma was made by one of the leading pathologists in the City, Dr. Norris being at that time unwilling to express an opinion.

The patient died January 31, 1907. The post-mortem examination was made on February 2, 56 hours after death. Only the chief features of the examination need be given here:

The body was that of a large male, 6 ft.  $\frac{3}{4}$  inches in height. On account of certain appearances suggesting acromegaly, more especially the form known as the *type carrée*, careful measurements were taken of the skull, face, hands, fingers and feet. In general, these indicated uniform enlargement of the fingers, especially of the right hand, and of both big toes. The significance of the enlargement of the right hand was, however, rendered difficult of interpretation on account of the existence of the old fracture of the left arm with atrophy of the muscles. The superior maxillary bones were enlarged and prominent. The lower jaw, nose and lips were normal in size.

The tongue, however, was large and broad, measuring from the epiglottis to the tip, 12 cm.; in breadth, 6.5 cm.; in thickness, 3 cm. The ears were symmetrical, very large and thick.

The abdomen contained several liters of clear fluid. A tumor mass weighing 1780 grams, was found in the upper median portion of the abdomen, displacing the stomach downward.

The left chest was filled with fluid, and the lung was collapsed. The right lung was voluminous, the bronchi containing mucopurulent exudate. Two of the bronchial lymph nodes were 4 to 5 cm. in length, and infiltrated with the tumor growth. The mediastinum was normal, with the exception of one small infiltrated lymph node. The thymus was absent.

The parietal pericardium was thickened and opaque, and showed small, raised nodules near the reflexion of the sac.

The heart was large, both ventricles hypertrophied. The mitral and aortic valves were slightly thickened. The aorta and vascular system presented no noteworthy lesion.

The liver weighed 1,580 grams. There was a moderate perihepatitis, with adhesions, and two small, firm whitish nodules about 3 to 4 mm. in diameter, were present beneath the capsule.

The spleen was small, fibrous, and firmly adherent to diaphragm, stomach and tumor mass. On its anterior border was an area of scar tissue which contained chalky material. Except for a large, left-sided varicocele, the genito-urinary tract was normal.

The kidneys were normal in size and appearance. The left suprarenal was large and firm, and contained a number of tumor nodules of varying size in the cortex

and medulla. The right suprarenal was normal. The tonsils were normal. The base of the tongue was somewhat glassy and smooth. The pharynx and larynx were normal.

**Stomach:** There was thickening of the muscular layers at the pyloric end of the stomach. About 2 inches from the pylorus, a large, teat-like process, with umbilication at the apex, was present. This was found to be composed of the greatly thickened muscular coats.

The small and large intestines were normal, except that on the posterior serous portions of the rectum there was a large whitish area, resembling inspissated purulent exudate.

All the cervical lymph nodes, especially on the right side of the neck, were greatly enlarged and infiltrated, forming packets which were adherent and continuous with the tumor mass occupying the right lobe of the thyroid gland.

The trachea and esophagus and the large vessels of the neck were practically embedded in the tumor mass and were compressed.

The left thyroid lobe was large but not involved. The right lobe, as referred to above, except for a few areas of normal thyroid tissue, was completely infiltrated.

The right axilla was almost completely occupied by large packets of lymph nodes, and several of the femoral lymph nodes on the right side were enlarged, the largest being about 3 cm. in length.

The tumor mass in the abdomen completely surrounded the pancreas, but the organ itself showed no involvement. The individual nodes were very large, firm, and adherent. The section was whitish and mottled with hemorrhagic foci.

The aorta and inferior vena cava, which passed

through the tumor mass, were greatly narrowed from compression.

The mesenteric nodes were small, yellowish in color, and not involved.

A striking picture was presented by the mesentery of the jejunum and upper ileum, upon which were situated a large number of small raised foci varying in size from a pin-point to the head of a small hat-pin. These nodules were yellowish-white in color.

The lacteals of the lower part of the small gut were injected and were the seat of small, whitish, dry and homogeneous foci.

The brain presented no gross lesions, except atheroma of the vessels and a small aneurysmal dilatation of the left vertebral artery. The sphenoid sinus contained thick, greenish-yellow purulent exudate. The middle ears were normal. The sella turcica and the pituitary gland were normal in size. On the inferior surface of the gland, a small, whitish nodule, 2 to 3 mm. in diameter, was present. This nodule was made up of tissue resembling in structure the neural lobe of the gland.

To recapitulate briefly, the case in its clinical aspects suggests a lymphosarcoma. Anatomically it likewise resembles a lymphosarcoma, the lymph nodes involved being the peripancreatic, cervical, axillary and femoral.

This diagnosis is, however, not borne out by the histological structure of the tumor which presents none of the characters of a lymphosarcoma or of a Hodgkin's or pseudoleukemia. No primary tumor was made out, although the involvement of the right lobe of the thyroid and the left suprarenal suggested such an origin. The possibility of a primary focus of growth in one of these organs may be eliminated, first, by the histological structure, second, by the anatomical picture presented; namely,



generalized lymph node involvement of widely separated groups of nodes, without involvement of the viscera. (It may be stated here that the small nodules beneath the capsule of the liver were not neoplastic in origin.)

Two distinct histological pictures may be made out: The first was presented by all the infiltrated lymph nodes. The second was quite distinct from the first, and was presented alone by the thyroid gland.

The structure of the predominant type of tumor is distinctly alveolar and non-vascular. The septa vary in thickness, in some places being broad bands of fairly dense connective tissue, in other places being delicate connective tissue fibrillae with prominent nuclei. This latter appearance is especially well seen in the smaller alveoli.

The alveoli are in the main filled with closely packed cells having large, round or oval nuclei containing little chromatin. The protoplasm of the cells stains poorly, is homogeneous and abundant. The cell outlines are indistinct and in places appear to be directly continuous with the stroma, which is in places distinct.

Although this description applies to a large number of the lymph nodes examined, a few show marked differences which must be referred to. In places where the tumor is more actively growing, the growth tends to lose its alveolar character, although the connective tissue septa are broad and hyalin. The large alveoli in such nodes show a peculiar picture, the central portion being made up of apparently necrotic material, that is, of cells staining deeply with eosin and having pyknotic nuclei and chromatin dust.

The layer of tumor cells bordering this portion is compressed and fused, forming a narrow line of demarcation beyond which the tumor cells not only show no

evidence of compression but are unusually large and protoplasmic. The stroma about this type of nodule is extremely scanty and shows numerous small lymph spaces packed with tumor cells; in fact, the tumor seems to have every resemblance to an endothelioma.

The tumor nodules in the left adrenal show practically the same structure as do the tumors in the lymph nodes, the masses of cells being packed in alveolar spaces of various sizes. In this organ, however, there are masses which stain a bright red with eosin and with Van Gieson's stain exhibit a deep orange. With the other anilin dyes and in iodine solution, no amyloid reaction was obtained in celloidin sections. The character of this material is uncertain, although it presents striking similarities to amyloid, or to a hyalin substance with a peculiar staining reaction.

The tumor situated in, or replacing, the right lobe of the thyroid gland presents a different structure from that described above. This tumor is composed of closely packed groups of cells in alveoli of different sizes. The connective tissue framework is in places abundant; the stroma finely fibrillated and edematous, containing numerous fibroblasts. In many places it is infiltrated with small round cells. The outlines of the tumor cells are ill-defined; the nuclei of the cells are large and oblong in shape, and tend to arrange themselves in concentric striae, somewhat resembling epithelial pearls. The centers of the larger alveoli are occupied by an eosin-staining material, broken down cells, and chromatin dust. The thyroid tissue has been completely replaced.

The nodules on the mesentery of the jejunum and ileum are inflammatory in character.

The area on the rectal serosa consists of an exudate with large round or ovoid cells and a few plasma cells

and leucocytes. A few Gram-staining bacilli were found in the sections.

The case we have described is therefore a tumor involving the peripancreatic and retroperitoneal lumbar lymph nodes, and the left suprarenal. All the cervical nodes were greatly enlarged and infiltrated, and also the right sub-maxillary gland, the right lobe of the thyroid and the axillary lymph nodes on both sides. The lymph nodes in the chest, except for two large bronchial nodes and one mediastinal node, were not enlarged. Except for a few nodules on the diaphragm, the pleural surfaces and the lungs were free from involvement. This lack of involvement would seem to indicate that the two tumor masses were of separate origin.

Only in the thyroid does one find any evidence of the invasive power of the tumor, the lymph nodes, although adherent, being discrete and not tending to coalesce. No metastases were present in the liver, spleen, kidneys, heart, lungs or bones.

Although the tumor corresponds anatomically to the usual form of lymphosarcoma, this correspondence does not extend to the microscopic structure.

We believe that it is best to consider the tumor a primary lymph node endothelioma, which form of tumor has been described as arising from the reticulum and endothelium of the lymph spaces. The evidently multiple origin of the tumor is a feature which we wish to emphasize.

In a search of the literature, only one report of a similar case has been found. Gallina,\* in 1903, described a tumor involving the cervical, retroperitoneal and mesenteric lymph nodes, and also both suprarenals. Gross section of parts of the tumor showed hyalin and

\* *Virchow's Archiv*, Bd. 172.

cystic changes, and microscopic examination of all parts involved led to a diagnosis of endothelioma, arising from the lymph glands and lymph spaces.

---

## A CASE OF BLASTOMYCOSIS.

GEORGE E. BREWER, M.D.

Dr. George E. Brewer presented a case of blastomycosis, giving the clinical history and the pathological report on the case made by Dr. F. C. Wood.

The patient was a young man, twenty-one years of age, of Russian birth, who had come to this country two years before. Eight months ago he had complained of pain between his shoulders which was increased on movement, and he was treated for muscular rheumatism. The pain, however, became worse, and he began to have a temperature. Two months ago he entered the Roosevelt Hospital for treatment. At that time he had a fluctuating swelling between the scapulae. A needle was introduced and a syringeful of dark colored pus was drawn out. It was thought that the condition was caries of the arch of the vertebra. An operation was performed, and on opening the abscess there was found a cavity which contained about six or seven ounces of dark colored pus, apparently mixed with blood. The spinous process of the third lumbar vertebra was distinctly involved. The second and fourth lumbar arches were also involved. The entire sac or wall of the abscess was dissected out, and the wound united by layer suture. The patient made a good recovery and the wound healed kindly. He remained perfectly well for about six or eight weeks

and then returned to the hospital with another fluctuating tumor over the first and second lumbar spines. This was larger than the first and there was considerable spinal rigidity. An incision was made and a large cavity was found filled with pus which was not mixed with blood. The abscess cavity seemed to be on the left side of the spine; one of the transverse processes was exposed and necrotic. The entire abscess cavity was again dissected out, and the patient did perfectly well for five or six days. There was apparently primary union in the wound. Two or three days later the wound was again dressed, after which the patient ran a temperature of  $102^{\circ}$  to  $103^{\circ}$  and the wound was re-opened. There was some retention of pus, and drainage was re-introduced. At the time of the report the patient had been normal for two or three days.

There had been practically no cough; a little sputum, however, was obtained by forced coughing, which showed nothing. There were no lesions of the skin and apparently no lesions in any other part of the body. The material was sent to the laboratory immediately after operation. Examination of the first syringeful of pus showed that the condition was one of blastomycosis. Afterwards the tissues were sent to the laboratory and cultures were made from them.

### *Pathological Report.*

The pus aspirated from the abscess cavity showed large numbers of spherical cells of different sizes, each surrounded by a clear gelatinous envelope. The fluid contained a large number of polynuclear and eosinophile cells, showing albuminous and fatty degeneration. These blastomycetes measured from 10 to 25 micra in



diameter. There was no evidence of budding in the organisms seen in the fresh pus. The wall of the abscess cavity was lined with granulation tissue and included a portion of the spine. The granulation tissue layer was about 1 cm. thick and was covered with a membrane of fibrin, leucocytes and red cells. In this membrane were embedded a considerable number of blastomycetes. The granulation tissue was very cellular, containing a moderate number of thin walled vessels and numerous polynuclear leucocytes. Scattered throughout the granulation tissue were many larger and smaller giant cells with nuclei ranged about the periphery of the cell and usually inclosing one or more blastomycetes. The inclosed organisms usually lacked a gelatinous envelope and also any internal structure. Frequently they were shrunken and evidently in process of destruction. The granulation tissue containing these organisms extended up between the muscle fibers of the spinal muscles and also invaded some of the fat tissue of the region. No organisms could be found in a small fragment of bone which was removed at the time of operation.

Cultures were made from the pus obtained from the first operation and an organism was isolated which grew easily though slowly on ordinary culture media. The formation of a mycelium in cultures was not observed.

### *Discussion.*

DR. JAMES EWING said that reports were steadily multiplying of cases of blastomycosis, or coccidioidal granuloma. The relation between these diseases was not yet clear, but most of them seemed to belong in the group of oidiomycosis. Of coccidioidal granuloma, Brown, in the *Journal of the American Medical Associ-*

*ation*, had recently collected nineteen cases; but he did not make it clear that all of them differed from oidiomycosis. The latter infection was more common, and Dr. Brewer's case seemed to belong to this group, since the organism showed budding forms in the tissue. Dr. Ewing said that Dr. Coley had under observation a similar case, the material from which had been studied at the Loomis Laboratory. This included a culture of the organism which was of the budding and mycelium-forming type, and hence an oidium. The increasing number of cases reported suggested that the disease was increasing in this country, though possibly the number of reports meant merely a more accurate diagnosis. The fact that in many cases there was pulmonary involvement indicated that this disease might be more infectious than had been supposed, and also suggested to surgeons that some care should be taken in handling it. In Dr. Coley's case the entrance was apparently through a wound in the toe. This patient had a cough with some bloody sputum, but no blastomycetes had been found in the sputum. This fact suggested that the infection might be through the blood, followed by the pulmonary involvement, and from there to different parts of the body. Dr. Ewing asked Dr. Brewer if he had been able to decide how the infection occurred in his case.

DR. BREWER said that in examining his case he had borne in mind that the greater number of cases reported so far had shown cutaneous lesions, but he had been unable to find any cutaneous lesions anywhere on this man's body, and repeated examinations had failed to show any lesions in the lungs. The case differed, therefore, from any case which he had thus far seen reported. Apparently the primary lesion was in the spine.

## AN EXPERIMENTAL STUDY OF CAISSON DISEASE.

HARLOW BROOKS, M.D.

The theories which have been advanced as explanatory of the symptoms of caisson disease are very numerous. They may be quite satisfactorily grouped, however, under three heads which comprise all the more probable explanations for the symptomatology and pathological anatomy.

I. *The theory of exhaustion and cold.* This theory has been chiefly propounded by Barella, Lampardarios, Jaminet, and Woodward. Triger also endorsed this explanation to a certain extent, assuming that the pains characteristic of the disease were rheumatic in origin and nature and were the results of the marked fall of temperature which takes place during locking out or decompression. As is well known, when the air pressure is lowered in the lock a considerable amount of cold is generated, even in warm weather, and the atmosphere of the lock becomes thick with fog and intensely cold. Jaminet, Woodward, and the others assumed that the conditions following the physical exhaustion incident to the work performed in the caisson caused extreme prostration and pains rheumatic in type. They claimed that the work was more exhausting because of the more rapid tissue metabolism which they assumed to take place as a result of the increased absorption of oxygen due to the compression or concentration of the air. They concluded that the cold generated in the locking out process acted particularly harmfully on account of this unnaturally exhausted condition of the body. Though this theory has now been abandoned by practically everyone, still it may be well to state a few of the more conclusive argu-

ments against it. In the first place the disease is quite as apt to develop in men such as foremen and overseers who perform little or no physical work; and the warming artificially of the outgoing lock has not resulted in a decrease in the number of cases. Furthermore, the statement that tissue metabolism takes place more rapidly under the compressed air is largely based on the premature conclusions of Jaminet that the urinary solids are markedly increased; and he assumed, entirely without proof, that this increase in solids represented an augmentation in nitrogenous waste products. No account was taken of the excretion by the bowel or skin and the theory is not even founded on correct or demonstrated primary assumptions. Contrary to the claims of this theory, workmen assert that exertion in the compressed air tires them less than in ordinary atmospheric pressure. It has also been shown that active exercise immediately after locking out prevents or lessens the severity of the symptoms. This theory of exhaustion has received no confirmatory evidence from experimental sources, and may now be entirely discarded.

II. *The theory of congestion and its sequelæ.* This theory has received the support of some of the most eminent workers, among whom may be mentioned Pol and Wattelle, Guerard, Limousin, and Andrew H. Smith. It is chiefly founded, apparently, on the gross pathological changes found. These, as has already been noted, are largely vascular in nature, congestion and hemorrhagic softening of the spinal cord and brain being the most constant lesions reported. Pol first showed that the danger of accident lay not in the increased pressure, but in the too rapid diminution of it. That Pol was quite correct in this statement is proven by the experiments of M. Hersent of Bordeaux (*Eng. News, Vol. XXXII*,

p. 67), who showed that the effect of excessive pressure extending up to 76.8 lbs., produced symptoms entirely different and distinct from those manifested in caisson disease; and it is now universally admitted that the rapidity of decompression is the essential producing factor. Smith states in addition that the length of time of exposure to pressure is also most important. This is doubtless true, but to a limited degree. For example, in the Brooklyn gas tunnel several donkeys were kept under pressure for nearly two years, the pressure at times reaching as high as fifty-two pounds, which I believe is the record of high pressure under which work has actually been carried on. Some of these animals were removed from the air rapidly; all such suffered or died from caisson disease; while those animals which were locked out in the same amount of time used for the men, came out entirely free (*W. I. Ames, Eng. News, Vol. XLI, p. 27*). This fact is of particular importance when we come to weigh the statement of Smith that long exposure of the superficial vessels to the support of the increased external pressure weakens the tone of these trunks so that on return to atmospheric pressure the vessels are unable to sustain the pressure of the normal blood. While it is beyond question true that during compression and also decompression considerable unbalancing of the circulatory function takes place, still that this is sufficient to cause the anatomical changes found post mortem has not been satisfactorily demonstrated. Finally, I have shown by the accurate determination of the blood pressure in a considerable number of cases, before, during, and after exposure to the increased atmosphere in the caisson, that but slight alteration in arterial pressure takes place, and, in so far as can be determined by our most accurate methods, the cardiac energy is



neither augmented nor decreased. It is manifestly impossible that any considerable difference can exist between the pressure within the body and that without, for were this the case collapse of such cavities as the abdominal must necessarily follow, a fact very well illustrated by tears of the membrana tympani where the Eustachian tube is imperforate. Catsario, from his experiments and observations, concludes that barometric pressure has no direct influence on the liquids in an organism, and an equilibrium of pressure exists throughout entire masses of blood. I feel that we are now quite safe in assuming that, after the tissues have become accustomed to the increased atmospheric pressure, say in twenty to forty minutes, no serious disturbance of the vascular distribution takes place, and we must look for some other explanation for the congestion and hemorrhage admittedly characteristic of caisson disease.

III. *The gaseous theory.* Briefly, this theory assumes that the blood, or the blood and tissues of the body take up an increased amount of air or gas proportionate to the amount of external pressure, which is liberated when the pressure is diminished. This theory in some of its forms has received the sanction of Bert, Boyle, Cassant, Catsario, Feltz, Francoise, Hoppe-Seyler, von Leyden, and many others. Bouchard attempted to explain the condition by the theory of compression of the intestinal gases, which acting like a great cup draws the blood from the other parts of the body, producing local anemia. This fanciful explanation I think does not even require discussion. Most of the observers believed that the increased gaseous content was due to absorption to a balanced point in the abnormally dense surrounding air. Boyle showed, by rapidly exhausting the air about animals confined in the chamber of the air pump, that bubbles of

gas formed in the blood and tissues, and that these animals died much more rapidly than animals simply deprived of oxygen. Hoppe-Seyler from similar experiments concluded that death was caused by pulmonary air emboli in these experiments and that the offending gas in caisson disease was largely or entirely oxygen. Bert, from experimental and clinical studies, accepted this doctrine, except that he assumed that the gas thus set free on decompression was nitrogen and not oxygen. In this relation we must consider Dalton's law, that the weight of a gas dissolved by any given fluid at a given temperature is directly proportionate to the pressure that the free gas exerts on the fluid. Assuming this to be equally true with the human body under compressed air, release from its excessive external pressure will naturally be followed by the liberation within the body of a bulk of air commensurate with the difference in pressure existing in the caisson and in the external atmosphere, and we should then expect bubbles of free air to be found within the tissues of the body under such circumstances.

The experiment of Smith which tends to show that the quantity of air absorbed by the blood is quite insufficient to produce serious changes in the body is invalidated, in my opinion, by the fact that he examined the blood alone, whereas in life all the tissues of the body are practically immersed in fluid. The earliest observations tending to substantiate this proposition are those of Heiberg (*Gazette med. de Paris*, 1878). In Heiberg's case, as also in one of Pol's cases the presence of gas blebs might be explained by post-mortem infection with such an organism as the *B. aerogenes capsulatus*. As already stated, however, Boyle, in 1670, produced bubbles of gas within the blood by rapid exhaustion of

air with the air pump. Francoise had suggested this possibility in 1860, after a study of his cases. Compliance with Dalton's law probably explains the variation in the rate of occurrence of caisson disease under the same pressure but with varying barometric conditions.

Bert, Catsario, and many others have confirmed these observations experimentally, and those of you who are familiar with the appearance of acute cases of caisson disease, either *in vivo* or at early post-mortem, are, I think, quite willing to accept the statement that such a liberation of free gas in the fluids of the body not only could, but does exist without causing air emboli and death in every instance. This is readily explained by the fact that the human body can withstand large quantities of air or nontoxic gas so introduced, as shown by the experiments of Magnin, Connolly, Feltz, Petit, Demarquy, and many others. This statement has been rather recently substantiated by experiments on air emboli conducted by Crile. Therefore, some explanation, aside from the mere presence of gas bubbles within the body must be supplied. Ames and others above mentioned attempted to explain this by the entirely untenable statement that carbonic dioxide poisoning results from the liberation of this gas, and that this toxemia is really accountable for the symptoms of caisson disease.

Bert asserted that nitrogen poisoning resulted from the liberation of this gas, while others have considered the symptoms due to excessive oxygen liberation. The symptoms and lesions produced, however, correspond to none of these toxemias, and the true solution was found by von Leyden in 1879. In the study of a spinal cord from a case of caisson disease, this scientist found minute lacerations of the substance associated with rupture of the small vessels, both of which changes he assumed to

be simply mechanical, due to the liberation of air bubbles in the tissues of the body. That lesions of this character, minute as they are, are quite sufficient to cause death when they occur in the brain or cord is, I think, beyond question. That they set up serious secondary inflammatory and degenerative processes in these organs which might thus act, appears to me entirely probable, and with a view to the demonstration of these lesions in caisson disease, I have performed the following experiments.

*Experiment I.* A strong flask containing 100 c.c. of distilled water was taken unstoppered into the compressed air lock. The pressure was then raised to 31 lbs., when the previously open bottle was tightly corked. The pressure was then slowly released and had fallen to five pounds above atmospheric when the cork was forcibly driven from the bottle. This experiment was repeated several times with the same result.

*Experiment II.* An egg and the body of a dead guinea-pig were taken into the lock, and the pressure was raised to 31 lbs. They were then placed in separate basins of water. During decompression, bubbles of air appeared on the surface, bubbling up through the water.

These simple experiments apparently demonstrate that under ordinary engineering pressures, sufficient air is released on decompression to indicate a considerable degree of absorption under pressure, by water and by the tissues of an egg or the dead animal body.

*Experiment A.* Three guinea-pigs, each weighing about 285 grams, were selected. Pigs A<sup>I</sup> and A<sup>II</sup> were killed with chloroform at the same time and in precisely the same manner.

Pigs A and A<sup>I</sup> were placed in the chamber of an air pump, A<sup>I</sup> being dead; and the air was exhausted rapidly so that in two minutes the mercury column stood at

25 mm. It was maintained at this height for two minutes, and then the air was admitted as rapidly as possible. After the first few strokes of the pump, pig A began to show signs of distress, running rapidly about; and very shortly both animals showed marked distention of the abdomen and to a lesser degree of the thorax as well. At the expiration of one and a half minutes, pig A threw himself on his back and with a few somewhat opisthotonic contractures ceased to breath. Meanwhile the distention of both animals was seen to be lessening rapidly. As the air was rapidly admitted, both pigs collapsed to much less than their normal bulk, and on removal from the receiver this condition still persisted.

Post-mortem examination of pigs A and A<sup>I</sup> showed no apparent difference in the bodies or viscera. There was superficial anemia in both and the internal viscera were somewhat congested. No bubbles of air were found in any part of the bodies. The membranes of the brain showed a slight congestion, no greater in one than in the other.

Post-mortem examination of pig A<sup>II</sup>, which had been killed simply with the chloroform, showed a slightly less degree of internal congestion.

The brains and spinal cords (inclosed in the vertebræ) of the three pigs were then placed in 5 per cent. formalin. The tissues remained in this for two days; they were then transferred to 80 per cent. alcohol, in which they remained for eight hours, when they were changed to 95 per cent. alcohol, in which they were allowed to remain for twelve hours. Small segments of the tissue were then selected and transferred to absolute alcohol in which they stayed for two and one-half hours. They were then transferred to chloroform for two hours, to chloroform saturated with paraffin for two hours, and



then to 52° paraffin for one hour. Sections were then blocked, mounted, and stained in the usual manner, the stains used being hematoxylin and eosin.

The brain from pig A showed quite marked dilatation of the blood and lymph passages, though for the greater part they were empty. The perilymph spaces were everywhere exaggerated, and in the white matter, notably in the internal capsule, there had apparently been an exudate of lymphocytes and polynuclear leucocytes between the nerve fibrils. The blood vessels seemed to be in a normal state as to the blood content. No air vesicles were present and no evidence of tissue laceration other than the widening of the perilymph spaces.

Sections of the spinal cord from pig A showed no alterations in the gray matter. The blood vessels were not congested; on the contrary, they seemed somewhat sparingly supplied with blood. The white matter showed quite frequent air vesicles, oval or circular in outline, and situated between nerve fibers, which had apparently been displaced. There was no apparent surrounding inflammatory reaction, and, for the greater part, these vesicles seemed to be empty, but a few contained small quantities of a serous exudate. The lesions were most frequent in the upper lumbar portions of the cord and in the anterior columns, along the anterior median fissure particularly. That these changes were not artefacts was apparently indicated by the fact that the nerve cells were not shrunken, and when stained by the Nissl method showed normal cytoplasmic pictures. Furthermore, the epithelial lining of the ventricle of the cord was intact and showed cilia very distinctly.

Section of the brain from pig A<sup>1</sup> showed practically

the same appearances as those seen in A, except that the distention of the perilymph spaces was less apparent.

Sections of the spinal cord of pig A<sup>I</sup> showed a normal structure throughout the cervical region, but in the lower dorsal and lumbar regions, the presence of air vesicles, particularly in the anterior columns, was shown. The degree of these was apparently not so great as in pig A; that is, the vesicles present were not quite so large and possibly not quite so numerous. Sections stained by the Nissl method, as well as those prepared in the ordinary way, seemed to indicate the absence of artefacts of any serious degree.

Sections of brain from pig A<sup>II</sup> showed a normal condition. The vessels were less congested than in the two previous specimens, and the distention mentioned in the perilymph spaces was not apparent. The sections were compared closely to the previous ones.

Sections of the spinal cord from pig A<sup>II</sup> did not show the presence of air vesicles, described in A and A<sup>I</sup>. Areas were of course present where the tissue had undergone more or less mechanical distortion, but the large spaces noted in the other cords were not seen.

*Experiment B.* Three guinea-pigs, each weighing 250 grams, were selected, all as much alike as possible. Pigs B and B<sup>II</sup> were killed with chloroform in the same chamber at the same time.

Pigs B and B<sup>I</sup> (B being dead) were placed in the receiver of the air pump and the air was slowly exhausted so that at the end of four minutes the mercury stood at 45 mm. The dead pig swelled somewhat, the living one considerably less. The breathing of the living animal became quite rapid and somewhat stertorous; after six minutes he fell on his side with the abdomen somewhat distended, still breathing rapidly.

The column of mercury was kept at the same level for eight minutes, the animal remaining apparently in the same condition, but the abdominal distention becoming less and less. Finally, the air was admitted quickly (15 seconds), and the animal, still breathing rapidly, was removed. After five minutes the animal began to attempt to rise, opened its eyes, and at the end of ten minutes seemed to be perfectly normal. About one hour later, the animal began to breathe rapidly and evidently with considerable effort; later it improved, but four hours after was not yet entirely normal.

The tissues from pigs B and B<sup>II</sup> were examined. There was a marked congestion apparent in the viscera of pig B, less marked in pig B<sup>II</sup>. The brains and spinal cords were removed and placed in 5 per cent. formalin, the cord, as before, being still inclosed in the column. The living animal recovered completely, being entirely normal on the next day.

The tissues B and B<sup>II</sup> remained in 5 per cent. formalin for forty-eight hours, when they were removed to 80 per cent. alcohol, after which the vertebræ were carefully cut away. After twelve hours they were transferred to 95 per cent. alcohol for six hours, and to absolute alcohol (small blocks having been selected) for four hours; to chloroform, three hours; chloroform paraffin, two hours; and 52° paraffin for twelve hours. Good sections were obtained and were stained with hematoxylin and eosin. Throughout the process the two groups of tissues were handled in precisely the same manner.

Selections from the brain of the control animal B<sup>II</sup> showed no shrinkage of the ganglion cells or other artefact. Blood vessels were moderately congested. The spinal cord from the same animal showed no change,

with the exception of slight laceration caused by an improperly sharpened knife.

The brain from pig B showed no observable changes. Blood vessels were for the most part empty or contained but scant amounts of blood. Apparently they were contracted. There was no ganglion cell shrinkage and nothing to indicate artefacts.

The spinal cord from the same animal appeared to be perfectly normal. In the lumbar portion there were a few vesicles between the nerve fibers and the same were present in less degree in the lower dorsal.

*Experiment C. October 15.* Two guinea-pigs were selected, C weighing 250 grams, and C<sup>1</sup>, 400 grams. Both were placed in the chamber of the air pump and the air was quickly (one minute) exhausted to 20 mm. where it was held for one and a half minutes. Both animals inflated rapidly, breathing became fast, and after one-half minute both keeled over, still kicking and struggling somewhat. The air was then admitted rapidly and the pump was started to remove the CO<sub>2</sub> and to force in fresh air. After five minutes both pigs revived and were able to stand. The vent was then closed and the air was again exhausted as before; but inflation of the bodies was much less apparent and the animals evidently suffered but very little, not losing station or consciousness. They were kept in this partial vacuum at 20 mm. for two minutes, when the air was again rapidly admitted. Collapse of the bodies immediately took place, but five minutes after removing them from the chamber they walked about and appeared to be free from pain; but twitching of the extremities was present in slight degree and some time elapsed before they seemed to be in perfect mental equilibrium.

*October 16.* Same experiment repeated with the

same result, the animals having been apparently in good condition in the meantime.

*October 17.* Same experiment; twitching more marked; lack of inflation at second aspiration marked. Recovery slower than on October 15 or 16.

*October 18.* Same experiment; both animals much exhausted after last aspiration. Abdomen collapsed on admitting air. Slight convulsive seizures on aspiration second time. Much exhausted, but revived after removal from chamber.

*October 19.* Animals sick since October 18. Experiment repeated; both much exhausted; breathing very rapid and convulsive after removal from chamber. The animals were not seen on October 20. They were active on the night of October 19.

*October 21.* Animal C (smaller) found dead. Internal organs congested; apparent rupture of the stomach as from a tear. Post-mortem changes general but of moderate degree. The brain and cord were removed and placed in 5 per cent. formalin, later carried through alcohol and so on as before. Animal C<sup>1</sup> was evidently sick; its hair was ruffled; it squealed if handled, and did not eat well.

*October 23.* Animal C<sup>1</sup> still sick; killed by chloroform; no gross lesions of internal organs. Tissues put in 5 per cent. formalin; technique as before. The animal was apparently better on October 22 and 23, but was still not well, and the action of the rear extremities seemed faulty.

Specimens were prepared for microscopic examination by the method before detailed, and in association with the organs of a control normal guinea-pig.

Animal C showed dilatation of the lymph spaces of the brain and cord. Occasional air vesicles were found,



particularly in the neighborhood of the blood vessels, but the specimens exhibited sufficient post-mortem changes to cause artefacts.

The brain of animal C<sup>1</sup> showed moderate congestion of the blood vessels. There was a slight leucocytic infiltration of the pia-arachnoid, and some of the blood vessels showed slight perivascular softening with small hemorrhages and edema. Recent karyokinetic changes were presented in the walls of some of the blood vessels. There was a general dilatation of some of the perivascular lymph spaces throughout the brain.

The vascular changes were more pronounced in the cord than in the brain, particularly in the dorsal and lumbar levels. Open spaces, apparently representing air vesicles, were found from place to place and were surrounded by areas of necrosed tissue. No ganglion cell changes were evident.

---

These experiments apparently show that when the air about either a living or a dead animal is quickly exhausted, air vesicles appear in the central nervous tissues, especially in the white matter of the spinal cord, associated with dilatation of the lymph spaces. Since these changes take place, though in slightly less degree, in dead tissues, it is fair to assume that they are mechanical in nature. The absence of lesions in control animals, the tissues of which were prepared in precisely the same manner, excludes the possibility of artefacts.

The symptoms produced by rapid exhaustion of the air are very similar to those of caisson disease, though complicated in these cases by deficiency in oxygen and the presence of CO<sub>2</sub>.

The swelling of the bodies, both of the living and of

the dead animals, on lowering the pressure, and their collapse on return to normal, shows that the pressure within the body corresponds to and varies with that of the surrounding atmosphere.

Experiments indicate that most of the symptoms evinced on rapid exhaustion of the air are due, not to abstraction of air *per se*, but to the effects of changes in the external and internal air pressure.

Frequent decompression from normal atmospheric pressure causes symptoms indicative of disease of the brain and spinal cord, and the appearance in these tissues of lesions of an inflammatory character, manifested by proliferation of the vessel walls, perivascular edema and necrosis, dilatation of the lymph spaces, occasional minute hemorrhages, and the formation of air vesicles, most numerous in the spinal cord; in brief, myelitis.

---

*Experiment D.* Two animals were selected, a small sized rabbit, animal D, and a guinea-pig, weighing 250 grams, animal D<sup>1</sup>. The animals were placed in the air chamber and compressed air was slowly admitted until at the end of eight minutes the pressure was 75 lbs. above atmospheric. The pressure was maintained at this level for sixteen minutes. The air was then allowed to escape rapidly (from 75 to 0 lbs. in one minute). The animals were removed from the chamber two minutes after release of pressure. Both were apparently in good condition and showed no evidence of suffering or disturbance. They remained in this normal state for three minutes, when the rabbit (D) suddenly became excited; breathing was rapid; and in one minute convulsive tremors of the lower extremities were noted. After

ten minutes there was paralysis of the hind extremities, more marked on the left side.

Animal D<sup>I</sup> began to breathe a little rapidly about five minutes after removal from the chamber, but apparently recovered shortly.

Four hours later animal D had apparently fully recovered. Slight disability of the left rear extremity could be detected on careful examination, but otherwise it seemed normal.

Both animals were killed by chloroform, and the tissues were placed in 5 per cent. formalin, then transferred to 80 per cent. alcohol, and handled as before.

Animal D (rabbit). The brain showed general dilatation of the perivascular lymph spaces. The blood vessels were generally congested. There was an occasional occurrence of air vesicles, particularly in the white matter, seen most distinctly where longitudinal sections of fibers were presented. Artefacts were excluded by control. There was marked dilatation of the perivascular lymph spaces. A few of these vesicles were apparently filled with lymph and a fine detritus. Others of them showed a probable relationship to the blood vessels and still others were surrounded by edematous and slightly lacerated tissue.

Animal D<sup>I</sup> (guinea-pig). The brain showed leucocytic infiltration with hemorrhage per diapedesis and small areas of necrosis and edema about some of the cortical and meningeal trunks.

The spinal cord showed vascular changes similar to those indicated in the brain. Occasional air vesicles were seen especially in longitudinal sections of the fibers. There was marked dilatation of the perivascular lymph spaces. The pericellular spaces in some instances showed enlargement from air vesicles.

*Experiment E.* Animal E was a small sized rabbit, animal E<sup>1</sup> a guinea-pig weighing 250 grams. The animals were placed in the chamber and the air was slowly admitted (six minutes) until the pressure reached 55 lbs., above atmospheric. The pressure was maintained at 55 lbs. for thirty minutes. The air was released in one minute. The animals emerged from the chamber apparently normal. After five minutes the rabbit began to breathe rapidly and convulsive tremors of the body were inaugurated; slight paralysis of the rear extremities resulted. The guinea-pig was apparently unaffected.

The animals were killed after fifteen minutes, by chloroform. No congestion of the superficial or internal organs was apparent. There were no gross lesions of the spinal cord or of the brain. The tissues were placed in 5 per cent. formalin and treated as before.

There was marked congestion of the vessels in the brain and cord of both animals with occasional hemorrhages of minute size, and dilatation of the lymph spaces. Air vesicles were present in both the brain and spinal cord, as in the specimens in *Experiment D*, but were less numerous and smaller.

*Experiment F, November 12.* Two rabbits, F and F<sup>1</sup>, together with two guinea-pigs, 'f' and 'f<sup>1</sup>', were placed in the air chamber. The pressure was raised from 0 to 75 lbs. in four minutes. Owing to leakage this was diminished to 60 lbs. in ten minutes. The pressure was released in thirty seconds. The animals were removed from the chamber after one minute, and were found apparently normal, except that the urine had been passed. After three minutes the animals began to show signs of distress, rapid respiration, trembling and staggering gait. At the end of ten minutes they had

apparently recovered. The vessels of the ears of the rabbits were of about normal size, though at first rather congested.

At the end of ten minutes the animals were replaced in the chamber and the pressure was raised to 60 lbs. in one and one-half minutes. They were kept at this pressure for fifteen minutes, and locking out was completed in thirty seconds, the animals being exposed in one and one-half minutes.

When first removed the animals showed no changes, but almost immediately the two guinea-pigs began to have rapid twitching of the extremities and rapid respiration, and finally, paralysis of the rear extremities. The rabbits a little later showed similar symptoms, but of more marked degree. Recovery began in fifteen minutes, and three hours later all appeared comparatively well except that the hair was rough and handling was evidently painful, and the tendon reflexes were greatly increased. The condition of the ear vessels were closely observed. Immediately after removal there was a congestion of the veins; this gave way to an arterial hyperemia; but after five minutes the vessels seemed to be normal.

*November 13.* All the animals were found in apparently normal condition. The tendon jerks of the rabbits were somewhat increased, but otherwise they seemed natural. Ate normally.

*November 14.* Animals in normal state. Rabbit F and guinea-pig 'f' transferred to *Experiment G*. Rabbit F<sup>1</sup> transferred to *Experiment H*.

*Experiment G, November 16.* A large rabbit, F, and a medium size guinea-pig, 'f', were placed in the air chamber, and compressed air was admitted up to 45 lbs., two minutes being occupied in locking in. The pressure



was maintained at this point for two hours. Locking out was accomplished in thirty seconds, and the animals were exposed in one and one-half minutes. The guinea-pig gave a few convulsive twitches, voided the urine, and died immediately, the abdomen inflating considerably. The rabbit was very cold, and soon began to have a swaying gait, terminating in partial paralysis of the rear extremities. He had rapid breathing and shook and voided urine and feces. The ears were very cold and almost bloodless. He remained in this condition for ten minutes when he began to show slow signs of recovery, finally breathing regularly and regaining the power to walk though at the end of fifteen minutes the gait was still very uncertain. He was then returned to the cage with the other animals.

At the post-mortem on the guinea-pig the superficial vessels were found to be anemic, while the internal viscera were congested. The cord and brain were removed and placed in 5 per cent. formalin; neither was congested, though the liver, kidneys, and spleen were.

Histological Summary. The brain showed numerous, very large sized air vesicles, apparently representing the greatly distended lymphatics and the perivascular lymph spaces. Some of the vessels showed proliferation of the endothelial lining. No ganglion cell changes were evident. In the cord the dilatation of the perilymphatic spaces was especially marked about the ganglion cells of the anterior horns.

The tissues were transferred to 80 per cent. alcohol and later treated after the usual manner for paraffin sections.

*November 17.* Rabbit F still showed marked increase of knee jerks, but ate well. No paralysis was evident.

*Experiment H, November 14.* Rabbit F<sup>1</sup> and a normal rabbit H, selected as of about the same size and weight, were placed in the air chamber. The air was admitted fairly rapidly so that at the end of three minutes the pressure stood at 70 lbs. Communication with the air tank was cut off. Leakage was slight, but the pressure fell somewhat and at the end of fifteen minutes the communication with the tank was again established to permit dilution of CO<sub>2</sub>; this process was repeated four times during the hour and the pressure was maintained almost constantly at 70 lbs.

After an hour the air was permitted to escape rapidly, so that the pressure fell in thirty seconds from 70 lbs. to 0. The animals were removed from the chamber in one minute from beginning of locking out. They were found in a condition of collapse; the bodies somewhat inflated, skin cold, large quantities of urine voided; temperature of chamber low. On removal from the chamber the ear vessels were very anemic, almost bloodless, and the animals showed convulsive seizures. They were not paralyzed, but suffered from tremors, evident dizziness and ataxia. After five minutes complete paralysis of the rear extremities had taken place, and a little later paralysis of the fore extremities. The animals lay helpless; the breathing was very rapid and shallow; the heart action was rapid and irregular.

At first the ear vessels were very anemic. This condition was soon followed by a very marked congestion which lasted but a few minutes, being replaced again by a very marked anemia with coldness. These vascular changes continued throughout the forty-five minutes during which the animals were closely observed. The changes from extreme anemia were more marked in rabbit F<sup>1</sup>, though they were also very apparent in H. The

waves of vascular alteration were not the same in the two animals, but each phase lasted usually from a few seconds to two minutes. The condition of absolute paralysis passed somewhat and the animals were able to use the fore extremities. In the rear extremities paralysis remained complete, and the mental condition apparently became steadily worse. Both animals had very cold skin, were unable to hold their heads up, and showed frequent convulsive seizures with spasms of twitching.

At the end of forty-five minutes from locking out, animal H was killed by a few whiffs of chloroform, as it was seen that recovery was impossible; respiration had become irregular, great vascular alterations still persisted, and the heart action was rapid. As soon as possible the spinal cord together with the brain was removed. The internal viscera were considerably congested; no air emboli were evident; and the dural vessels of the cord were very markedly congested; but though there were apparently areas of softening in the spinal cord, no spinal hemorrhages were macroscopically demonstrated. The vessels of the brain were moderately congested, and no areas of softening were evident.

The tissues were immediately placed in 5 per cent. formalin and were subsequently handled after the usual method.

One hour after locking out, animal F<sup>I</sup> was found to be dying. As soon as respiration had ceased the tissues were removed after the usual method, and were found to show exactly the same conditions seen in animal H. Tissues of this animal were handled in the same manner as those of H.

No provisions were made in this experiment for the disposition of CO<sub>2</sub>, except that the communication with the entire tank of compressed air was frequently

opened. As animal F in experiment G had recovered from similar conditions it was thought that the amount of  $\text{CO}_2$  did not influence the result to any appreciable degree.

*Experiment I, November 25.* Rabbit F, together with a smaller rabbit I, was placed in the compressed air chamber, and the pressure was increased from 0 to 60 lbs. in one minute. The pressure was maintained at that grade for forty-five minutes, frequent communication with the entire tank being opened for dilution and  $\text{CO}_2$  poisoning. Further, an abundant supply of fluid NaOH was placed in the chamber. The air was released rapidly, the pressure falling to 0 in thirty seconds, and one minute was taken in releasing the animals. The animals were removed from the chamber in a dazed condition, and in a few minutes paralysis of the extremities and of the back was marked, and the breathing rapid. The ears became rhythmically congested and anemic, the animals were very much distressed, and at times spasmodic trembling of the entire body took place. These symptoms continued for three hours, becoming then slowly less marked and finally disappearing on the next day, though the animals were not well. The large animal showed the less pronounced symptoms.

*November 27.* The animals were apparently well, and the experiment was repeated in all details, except that the maximum pressure was 45 lbs. Symptoms were less marked and the paralysis was more pronounced in the fore extremities. Recovery was more rapid than before, but animals were profoundly affected.

*December 2.* Rabbits F and I were placed in the chamber and pressure was raised from 0 to 90 lbs. in six minutes. The animals were left in this pressure for thirty minutes. The pressure was then gradually diminished by allowing the slow escape of the air, so that in ten

minutes it had fallen to 0. The animals emerged from the chamber apparently undisturbed, and showed no symptoms either then or later which would tend to indicate that the pressure had been at all deleterious.

*December 5.* The animals had remained in a normal condition, and both had gained in weight. Both animals were placed in the chamber, and the air was slowly admitted so that at the end of six minutes the pressure had risen from 0 to 110 lbs. The pressure was maintained at this point for sixty minutes. The air was then permitted to escape very rapidly, so that in thirty seconds the pressure had become 0. The chamber was opened one minute from the end of the locking out. The animals stepped from the chamber as though in normal condition, except that the breathing was not as slow or regular as natural. They walked about the room, appearing to be somewhat excited, but not showing any signs of paralysis. At the expiration of three minutes, the animals almost simultaneously became very much excited, and the ears became pale. Previous to this they had alternately paled and flushed, but this was much less marked than in the previous experiment.

The pupils were distended, the eyes bulged from the head, and the head was thrown rhythmically from side to side. The neck muscles stiffened; spasmodic twitchings of the rear extremities came on followed by paralysis, apparently beginning from behind and extending forward; finally paralysis involved all of the extremities, and the animals fell to the floor. The action of the heart was irregular and weak. The smaller animal succumbed first and was dead in five minutes from the beginning of serious symptoms; while the larger animal lived slightly longer and died suddenly, giving forth cries.



As soon as the animals were certainly dead the cavities were opened and it was at once noted that the vessels of the omentum and mesentery were much congested. In the smaller animal they contained numerous bubbles of air, while the subcutaneous tissues were also emphysematous to a moderate degree. The subperitoneal fat, particularly that about the kidneys, was riddled with gas blebs, and the peritoneal coat of the gut in many places was raised into tiny blebs. The entire gut was considerably distended but no ruptures had taken place. The lungs were very emphysematous, particularly in the smaller animal. The cord and brain showed no gross lesions. The liver was congested in both cases, but no emphysema of this organ was evident. There could be no doubt as to the presence of air bubbles in the tissues and blood vessels, and when the trunks were cut the blood which escaped from them was literally red foam.

The brain and spinal cords were removed in the usual manner and at once placed in 5 per cent. formalin, where they remained for twenty-four hours. They were then gradually removed to 80 per cent. alcohol, remaining in this for twenty-four hours. The spinal vertebræ were removed, and after having been again placed in 80 per cent. alcohol, the cords and brain were segmented and the portions chosen for examination were transferred to 95 per cent. alcohol for eighteen hours, after which they were placed in absolute alcohol for three hours, transferred to chloroform for six hours, chloroform saturated with paraffin for eighteen hours, and paraffin for three hours. They were then sectioned.

When these sections were blocked it was found to be very difficult to remove the bubbles from the specimens, which behaved exactly as specimens of lung tissue when handled in the same manner. For this reason the tissues

were reblocked several times. The result, however, was bad in each case and the sections obtained were not as smoothly cut as was usually the case. For this reason, and because the lesions found in these specimens led me to think of possible errors of technique which had given rise to very pronounced artefacts, I carried other blocks of the same tissue through collodion, in a similar manner, using the greatest care to avoid artefacts, the tissues being allowed to remain in absolute alcohol and in thin collodion but a very short time. As the lesions found in both sets of specimens were identical, I am justified in the conclusion that the changes were not brought about by faulty technique in their preparation.

Rabbit H. Microscopic Examination. The brain showed marked dilatation of the lymph spaces. There were a few microscopic areas of hemorrhage in the meningeal or cortical vessels, and very marked dilatation of the perivascular and pericellular lymph spaces. Many of the vessels were markedly contracted. No ganglion cell changes were present. The spinal cord showed perivascular and vascular changes like those in the brain. The alterations were apparently most marked in the dorsal levels.

Rabbit F showed no changes exactly like those detailed in rabbit H, except that in addition to dilatation of the lymph spaces and minute hemorrhages into the air vesicles, many of the smaller trunks were surrounded by leucocytic infiltration and by more marked edematous and necrotic changes in the tissues; and the endothelium of certain of the vessels showed marked proliferation.

Rabbit I. The brain showed changes noted in the other animals, but to even more marked degree, in addition to interstitial hyperplasia about certain of the vessels.

*Experiment J.* A medium size rabbit was placed in the air chamber, the usual precautions being taken to prevent CO<sub>2</sub> poisoning. The pressure was raised in six minutes from 0 to 100 lbs., at times rising to 110 lbs. This pressure was maintained for 45 minutes, at the end of which time the air was allowed to escape slowly so that at the end of ten minutes the pressure was 0. The animal emerged from the chamber apparently unaffected and continued in normal condition.

### *Conclusions.*

The conditions existing in the production of true caisson disease have been closely simulated in my series of compression experiments with, however, the omission of physical exercise. The fact that the resulting state closely resembles true caisson disease indicates then that exertion or physical exhaustion is at least an unessential factor in its production.

In all the hyperpressure experiments the stage of compression or locking in was productive of no serious symptoms or lesions, even when the pressure extended up to the enormous figure of 110 lbs. above atmospheric (*Experiments I and J*). In human beings, however, it is doubtless true that these excessive pressures can not be endured, as demonstrated abundantly in practical work as well as by the experiments of Hersent, only one of whose subjects was able to sustain the pressure of 76.8 lbs.

The length of time under pressure appears to be an important factor in the production of the disease, as first stated by Smith, and indicated especially by *Experiment G*. This is probably accounted for by the more complete absorption of the compressed air, and

consequently the greater difficulty in liberation on decompression.

Serious or fatal symptoms appear only on too rapid decompression, and this appears to be the one absolutely essential factor in the production of the lesions. This is especially indicated by comparison with the exhaustion experiments *A, B and C*. This observation is in thorough accord with the best clinical statements in regard to this important fact.

The condition of the air of the compression chamber appears to furnish no essential agents toward the production of the disease. In practice this can, however, be but partly true, for unquestionably the presence of  $\text{CO}_2$  in excessive amounts, or of such foreign materials as illuminating gas, fire damp, and soot, as found in the early caisson work, in the first use of the diving bell, and of course where free oxygen is deficient, causes secondary depressing conditions which can not fail to have a great clinical bearing.

The essential anatomical lesions found in both acute true and acute experimental disease are identical. They consist of dilatation of the lymph channels, the presence of free air vesicles or lacerations resulting from the liberation of air in the vessels and in the soft tissues, notably in the spinal cord and brain, and of capillary hemorrhages. Hemorrhage per rhexam has never to my knowledge been reported in caisson disease.

Exactly similar changes, varying only in degree, are produced by rapid exhaustion of the air, thus excluding the theory of gas toxemia. My experiments (*A, B and C*) in this research thus substantiate thus performed by Boyle in 1670. These lesions are produced alike in the living and dead body; they are, therefore, probably mechanical and not pathological in origin (*A, B and C*).

Air under compression is absorbed by inert fluids (*Experiment 1*) by certain inert tissues (*Experiment 2*), and by dead and living animal tissues (*Experiments A to J*), and the amount of absorption depends largely on the degree of compression, probably complying with Dalton's law. On release of the pressure, air is liberated from these substances in quantity according to the degree of previous absorption (*Experiments D to I*).

When rapid liberation takes place in dead or living animal bodies, it causes the dilatation of the lymph passages, the rupture of capillaries, and the production of tissue laceration by the escaping air bubbles. Frequent repetition of these lesions in the living tissues causes endothelial and interstitial proliferation in and about the diseased vessels and eventually secondary inflammatory changes. (*Experiments C, H and I*.)

The symptoms of true caisson disease admit of the above causative explanation, and the paralysis and symptoms of spinal and cerebral disease are produced in this manner. They are followed in subacute or chronic cases by secondary degenerative and inflammatory lesions which may be grouped as myelitis (*autopsy reports*).

Finally, from the pathology of true and experimental caisson disease, we are justified in concluding that the essential productive factor is the rapid liberation of air from the fluids and tissues of the body when decompression is allowed to take place too rapidly. This liberation of bubbles of air causes laceration of the soft tissues, dilatation of the lymph spaces, and capillary hemorrhage.

### *Discussion.*

Dr. O. H. SCHULTZE said that he thought all would subscribe to Dr. Brooks' conclusion that the primary



cause of death, where this occurred after coming out of the caisson, was too rapid decompression. In speaking of the presence of gas in the body, Dr. Schultze said that he had seen cases at autopsy where the right ventricle was so distended that on opening the heart under water there was an ebullition of gas which practically amounted to an explosion. In one case, at least one-third of the contents of the right ventricle was gas. The lungs in some cases showed very intense congestion; in other cases, where there was a large gas content in the right ventricle, the lungs were extremely pale and emphysematous. The cases varied considerably in regard to the amount of cellular emphysema which occurred. The first case which Dr. Schultze had autopsied had shown a very marked cellular emphysema in the appendices epiploicæ. In cases dying several hours after decompression or perhaps one or two days after, in which event no gas would be found in the blood, the cause of death might be difficult to determine. In two cases which he had seen, the examination of the spinal cord showed small hemorrhages scattered throughout the cord, and this might explain why some of these patients later develop paraplegia. In regard to the ecchymoses which were occasionally seen, these might be due to the mode of death. In one case which Dr. Schultze had examined, of death following too rapid decompression, both middle ears were filled with blood. This evidently was a case where there was a direct rupture of vessels.

Dr. A. WADSWORTH asked Dr. Brooks whether in the lesions which he had examined there were any signs of the liberation of gas within the cells.

Dr. BROOKS said that he did not know. He had been so sceptical about artefacts, that he had not felt sure whether many of the findings were due to the effects

of the air or whether they were artefacts. He had performed personally only two autopsies on cases of human caisson disease. Both of these had died of pulmonary embolism. He had thought the embolism in these cases was probably due to softening of the spinal cord.

---

## ON THE INFLUENCE OF TISSUES, CHOLESTERIN AND CHOLESTERIN ESTERS UPON THE PRODUCTION OF TETANOSPASMIN AND TETANOLYSIN IN FLUID CULTURES.

HIDEYO NOGUCHI, M.D.

In an anaerobic culture of *B. tetani*, tetanospasmin and tetanolysin develop simultaneously. The amount of lysin in such cultures is, as a rule, small when compared with the amount of spasmin, and can be disregarded in the fatal issue which follows tetanus intoxication. But, so far as I am aware, there has been no direct evidence brought out for this assumption, and a separation of tetanospasmin and tetanolysin in a culture of *B. tetani* has never been effected. In the present study I have succeeded in obtaining a culture, which, while rich in spasmin, possessed no hemolytic principle. The experiment also may illustrate the mode of the toxin production of *B. tetani* in the animal body. I have cultivated *B. tetani* in bouillon containing portions of fresh or boiled animal tissues, and cholesterolin or various esters of cholesterolin, and have then examined them for these two active principles. The result can be summarized as follows:

*The addition of fresh or boiled tissues.* To ordinary plain or 0.5 per cent. glucose bouillon, a small portion of sterile organs (liver, spleen, kidney, of rabbit or guinea-pig) was added. Two series were prepared, one raw and the other boiled for five minutes before inoculation with *B. tetani*. After inoculation, the two series were cultivated both anaerobically and aerobically at 37° C. for two weeks. The controls, with plain or glucose bouillon, but without the addition of tissues, were cultivated anaerobically.

Growth was abundant in tubes with tissues, and less in the controls. Microscopically, there were numerous spores in the former, but almost none in the latter.

Examination for toxicity and hemolytic power was made. Rats were employed for the determination of toxicity (subcutaneous), and the washed corpuscles of the rabbit for the lysis. The minimal lethal dose of the control cultures was found to be 0.001 c.c., and the minimal dose for complete hemolysis for 2 c.c. of a 5 per cent. suspension of the washed blood corpuscles, 0.04 c.c. The toxicity of the anaerobic cultures of tissue bouillon (both raw and boiled), was 0.001 c.c.; that is, exactly the same as the controls; but none of the tissue cultures exhibited hemolytic activity.

The bouillon culture containing tissue grew aerobically just as well as the anaerobic series, and formed numerous spores. The toxicity of the aerobic culture was, however, decidedly inferior to the anaerobic. It required 0.1 c.c. to produce death in six to eight days; but 0.01 c.c. failed to kill the animal although it produced marked tetanus and subsequent exitus from emaciation after a long period (thirty days in one case.) No hemolysin developed in the aerobic cultures with tissues.

*The addition of cholesterin and cholesterin esters.* Cholesterin (Merck) and its various esters, including palmitate; stearate, and oleate, as prepared after the method given by Hürthle, were employed. None of these preparations is soluble in bouillon. Cholesterin and

cholesterin palmitate can be suspended fairly evenly, but after long standing sink to the bottom of the vessel. Stearate and oleate of cholesterin are higher and float to the upper layer of the fluid. Four-tenths (0.4) of a gram of each preparation were mixed with 30 c.c. of plain or 0.5 per cent. glucose bouillon. After inoculation with *B. tetani*, these were cultivated anærobically at 37° C. for three weeks. The result is summarized in the following table.

Culture Media	Growth	Sporulation	Toxicity (Rat) 1 m.l.d.	Hemolytic power (Rabbit corpuscles) 1 m.h.d.
Plain bouillon .....	good	slight	0.003	0.05
Glucose bouillon .....	good	slight	0.003	0.05
Plain bouillon + Cholesterin .....	good	much	0.003	negative
Glucose bouillon + Cholesterin .....	good	much	0.003	negative
Plain bouillon + Cholesterin palmitate...	good	much	0.003	0.5
Glucose bouillon + Cholesterin palmitate...	good	much	0.003	0.5
Plain bouillon + Cholesterin stearate ....	good	much	0.003	0.05
Glucose bouillon + Cholesterin stearate ....	good	much	0.003	0.05
Plain bouillon + Cholesterin oleate .....	good	slight	0.003	0.04
Glucose bouillon + Cholesterin oleate .....	good	slight	0.003	0.03
Plain bouillon + Fresh tissue .....	good	abundant	0.002	negative
(Rabbit liver)				
Glucose bouillon + Boiled tissue .....	good	abundant	0.002	1.0
(Rabbit liver)				

From this table it will be seen that the presence of cholesterin and various esters of cholesterin in fluid media does not interfere with the growth and the production of spasmin of *B. tetani*. On the other hand, cholesterin, when added in sufficient amount, removes all hemolytic principle which may have developed in the media. Contrary to cholesterin, cholesterin esters have no neutralizing property against tetanolysin, although cholesterin palmitate appears to be slightly antagonistic to this principle. In this series it was also found that the presence of raw tissues in a culture removes the hemolytic principle more completely than does the boiled.

#### *Discussion.*

Dr. C. W. FIELD asked Dr. Noguchi whether, since it seemed that with the cholesterin oleate more hemolytic principles developed, he had tested the oleate in the broth as to its hemolytic properties, and also whether he had tried any inorganic substances which would take up oxygen from the fluid. He believed that the animal tissues were oxydized and thus the medium was more strictly anaerobic.

Dr. NOGUCHI replied that cholesterin oleate is slightly hemolytic by itself, and a slightly higher hemolytic titer of the culture containing this preparation might be explained by this fact. No inorganic reducing agent had been tried. The essential point of the present work was a successful separation of tetanolysin and tetanospasmin in a fluid medium by means of cholesterin or animal tissues.

---



## PATHOLOGICAL INVESTIGATIONS.

MARY A. DIXON JONES, M.D.

Dr. Mary A. Dixon Jones discussed the relationship between fibroid growths and metabolic processes.

A CASE OF ANEMIA DUE TO BOTHRIO-  
CEPHALUS LATUS.

H. L. LYNNAH, M.D.

Dr. H. L. Lynnah exhibited a specimen of tapeworm of the species *Bothriocephalus latus*. He called attention to the fact that *Bothriocephalus anemia* is rare in this country, and said that the worm is not found in the stool except in rare instances. The specimens are usually derived from immigrants from the Baltic coast provinces of Finland and Poland. Only a small proportion of the hosts show an anemia, though it has been demonstrated that the *Bothriocephalus* is capable of producing severe anemia, and that after expulsion of the worm the person suffering from the anemia may regain perfect health. The patient from whom this worm was obtained was a young man, a Swede, twenty-five years of age, who was suffering from a severe case of tonsillar diphtheria. It was evident from his appearance that he had an anemia of the pernicious type. There was a hemic murmur over the heart. The red cell count was 1,300,000, white cells, 13,000; no eosinophiles. There was moderate poikilocytosis. A few red cells showed granular degeneration and there was moderate polychromatophilia. It was thought that the anemia might be a consequence of the diphtheritic process. The absence of eosinophilia

was misleading as in general intestinal parasites incite an eosinophilia, the one exception being the *Bothriocephalus*, though occasionally eosinophiles are seen in connection with this parasite. A segment of the worm was, however, found in the stool, and the next day the whole parasite was expelled with the exception of the head which was lost. Dr. Lynnah suggested that in some cases the absence of eosinophilia might be important as indicating the presence of *Bothriocephalus* when a specimen of the worm could not be obtained. The increase in the leucocytes in the blood in this case was undoubtedly due to the diphtheritic infection. A short time after expulsion of the worm the red cells increased to 2,250,000, and the hemoglobin ran up twelve points.

# Proceedings of the New York Pathological Society.

---

NEW SERIES, Vol. VII.

APRIL and MAY, 1907

Nos. 3 and 4

---

## TABLE OF CONTENTS

BIERWIRTH AND BROOKS, A Case of Streptococcus Sepsis.—PAPPENHEIMER, A Case of Septicemia, probably Gonococcal in Origin.—GIBNEY, A Case of Compression Paraplegia.—SABEL AND SATTERLEE, A Case of Acute Lymphatic Leukemia.—JANEWAY AND WAITE, A Case of Syphilis of the Heart.—THRONE, Specimen showing Rare Sequelæ of Intubation.—LE WALD, A Case of Bilateral Supernumerary Index Finger Replacing the Thumb. The presence of Amebæ in the Mouths of Healthy Individuals.—ZINSSER, Experimental Blastomycotic Lesions.—WADSWORTH, A New and Convenient Desk Bath for Opsonic Work.

---

DR. CHARLES NORRIS, *President*.

---

## A CASE OF STREPTOCOCCUS SEPSIS.

J. C. BIERWIRTH, M.D., AND HARLOW BROOKS, M.D.

Dr. J. C. Bierwirth reported the clinical history of a case which was of interest primarily in view of the short duration of the illness. The patient was a woman in her fortieth year who had previously enjoyed good health and who had been under his personal care for about ten years. There was nothing unusual in her previous history except an attack of rheumatism some three or four years before, which had been rather slow in

yielding to medication. As a consequence she had some heart murmur of a mild character. She was the mother of three children, the youngest of whom was seven years of age. On February 23, she first complained of feeling ill with no particular symptoms except fever, headache and a slight sore throat. Her temperature was  $101^{\circ}$ . Examination of the throat showed a slight reddening of the anterior pillars, nothing more. She had a good deal of sore throat in connection with her previous attacks of rheumatism, but of a much more severe character. Acetanilid was prescribed. At ten o'clock the next night her temperature was  $105^{\circ}$ , and she complained of severe headache and general aching of the body, and was rather nervous. Five grains of acetanilid were again prescribed. On February 25, the patient's temperature was  $103^{\circ}$ . There were still no other symptoms except headache and general malaise. It seemed certain that the case was one of influenza. Aconite was given to make her more comfortable. On February 26, the patient had a temperature of  $104^{\circ}$  and complained of soreness in the index finger of the left hand, which suggested that possibly some latent rheumatism had been set free by the infection. She was given four doses of five grains of aspirin, which resulted in profuse sweating in the afternoon. Her temperature, nevertheless, remained  $104^{\circ}$ . The patient then complained of very severe pain in the legs, and very careful examination of both legs was made. Nothing abnormal was found either by sight or by touch. A hypodermic of morphine was given and a nurse was secured, as the patient then for the first time looked ill. This might have been due to the continuation of the fever or to the acute pain which she was suffering. The temperature that night was  $105^{\circ}$ , later it rose to  $105.6^{\circ}$ ; in the morning it was  $104.5^{\circ}$ . During the night, the

patient, in spite of the hypodermic, complained of pain in her legs, although she was inclined to sleep. The pulse was weak and irregular and there was some slight incoherency of speech at times. The patient was extremely restless. After a sponge bath the temperature fell to 104°. At seven o'clock in the morning of February 27, the patient was much worse; the pulse was very weak and difficult to count. There was also a discoloration on the instep of the left foot which looked like a bruise. This had not been there the night before. At eight o'clock the pulse became imperceptible at the wrist though the femoral pulse could still be felt. Digitalis and strychnin were given as stimulants. The discoloration of the foot spread rapidly. When seen at twelve o'clock the patient was evidently dying. She presented the picture of a person who is bleeding to death, with pinched features and blue lips. Both legs looked almost gangrenous below the knee. They were very hard to the touch and were covered with large watery blebs which extended up on the calves. Saline enemata were ordered and the stimulation was stopped. Dr. Alexander Lambert was called in consultation during the afternoon. When he reached the bedside the patient was clear in her mind but died within ten minutes. The clinical history of the case was an absolute puzzle. In the afternoon permission was fortunately secured for a post-mortem.

\*            \*

Dr. Harlow Brooks reported the results of the autopsy on Dr. Bierwirth's case.

Post-mortem about four hours after death. The general appearance of the body was that of a person who had bled to death, the skin being the peculiar black and



white color seen in these cases. The arms and hands were absolutely waxy. The legs showed what looked like a moist gangrene. There were blebs over the backs of the calves and along the sides. Puncture of these gave exit to a blood stained serum. Rigor mortis was very pronounced throughout the body. Purpuric spots were looked for but were not present. The organs showed normal structures. The lungs showed edema and slight congestion; the heart looked perfectly soft and had practically no blood in it. There was no blood in the veins of the vena cava or of the lungs. The liver was washed out; there was no blood in the large veins there. The kidneys were white and apparently normal except for the anemia. The mesenteric vessels were notably anemic. The spleen was the only organ which was apparently diseased. It was enlarged about one volume, was deep purple in color and soft in consistency, and presented a mulberry appearance. Cultures were taken from the spleen and from the small amount of blood in the heart. There was no enlargement of the lymph nodes in the neck or of the thoracic and mesenteric nodes. The intestine was gone over from the esophagus to the anus, and nothing was noted except a most striking absence of food. The intestine was absolutely clean. There were no ulcerations. The pancreas was normal. There were slight adhesions around the Fallopian tubes and very slight around the fundus of the uterus. One ovary contained a rather large hemorrhage. There was a marked softening of the right adrenal body. This was as soft as the adrenal usually is several days after death. It was thought to be hemorrhagic softening. The left adrenal seemed to be normal except for fatty infiltration. Incision into the calves, which felt as hard as pieces of wood, showed nothing in the skin ex-

cept the blebs. Beneath the skin there was nothing but blood. The vessels showed no actual rupture, but there seemed to be a diffuse hemorrhage from diapedesis. The arteries seemed to be normal.

The anatomical findings therefore were: Septic condition of the spleen, marked softening of the right adrenal body; and hemorrhage into the muscular tissues of the legs. Cultures from the spleen showed pure culture of streptococcus. This culture was unfortunately lost before its virulence could be studied.

Dr. Brooks was inclined to look upon the case as one of streptococcus sepsis following a mild angina; but the lesions were not those of sepsis and the clinical symptoms were not.

As concerned the lesions found in the adrenal body Dr. Brooks said that the right adrenal was practically destroyed. It showed areas of small round cell infiltration and marked destruction of cells which he took to be parenchymatous degeneration. The left adrenal body showed changes of the same character only differing in degree. A great many cells were practically broken down and dissolved out. Some of them showed degeneration. Many of the veins were filled with leucocytes. Theoretically, Dr. Brooks thought that the case was one of streptococcus infection, such as not infrequently occurs after a mild angina. He believed that early in the infection there was a focus in the adrenal body, causing softening, and that the removal of the adrenal secretion from the circulation resulted in the fall of blood pressure. This was borne out by the feeble pulse; for ten minutes before death no radial pulse could be felt. He was therefore inclined to think this an instance in which localization of the septic lesion in the adrenal body led to a remarkable fall of blood pressure, and that as a re-

sult the blood went into that portion of the body most distant from the central portion, and stayed there simply because there was nothing to push it back. There was no capillary pressure.

### *Discussion.*

DR. JAMES EWING expressed his admiration for Dr. Brooks' courage in attempting to explain the condition as he had, though he might not be willing to follow him to a definite conclusion that the lesion of the adrenal worked in the way he had described. Dr. Ewing asked whether Dr. Brooks had considered the possibility that a lodgment of bacteria in the points distant from the heart had had something to do with the condition of the legs. Dr. Ewing also asked whether the blood had been examined during life for anemic or toxic changes in the red cells. He thought that in a case of this sort the true explanation could be reached only after the consideration of a great many factors, each one by itself incompetent to produce the result, but when combined able to bring it about.

DR. E. LIBMAN asked whether there was any abnormal condition of the blood before the patient had been taken ill. Of course, if a blood culture had been taken during the course of the clinical history the whole case could have been more easily explained. In chronic affections of the adrenals he had seen a tendency to disseminated hemorrhagic rashes, but he had never seen a case in which the condition was localized in one part of the body. He did not think it necessary to explain the case by the absence of adrenal secretion because the other adrenal had been normal and probably was able to produce sufficient secretion. The effect might be pro-

duced by the sympathetic nervous system (in this case plus the probable toxic condition).

DR. O. H. SCHULTZE said that the theory which Dr. Brooks had formulated, that the condition was due to a sudden fall of blood pressure, seemed to him rather curious. In cases of death from hemorrhage, where there was of course a fall of blood pressure, it was surprising to note on autopsy the amount of venous stasis throughout the organs, even when two or three pints of blood had been lost. That the blood should collect in the legs when a person was in a recumbent posture seemed to him unlikely.

DR. BIERWIRTH said that he would like to add that in this case he had happened to know all about the patient's general condition. She was a very nervous woman; but physically she was in excellent health, so that there was no reason to make a blood examination. The clinical history was like that of many cases of influenza which he had seen, and there was nothing in it to lead one to suspect a serious disease. The patient had certainly not been anemic. Dr. Bierwirth had discussed the clinical features of this case with a number of physicians and had yet to find one who had ever seen anything like it, or who could give any explanation of it. The throat infection was extremely mild; there was no congestion; the tonsils and the glands of the neck were not enlarged. There was simply headache, fever, and pain in the legs, until something suddenly happened and the patient died in less than twenty-four hours, with all the blood in her legs.

DR. T. C. JANEWAY said that the occurrence of the pain in the legs before the appearance of the discoloration suggested to him that this might possibly be a case of thrombophlebitis. There might have been a throm-

bosis which occurring in the presence of a streptococcus septicemia might have resulted in softening and bleeding into the legs.

DR. BROOKS said that he had of course thought that the condition might be due to thrombus, and for that reason he had almost torn the calves to pieces in trying to find the veins which were thrombosed; but he had been unable to find these. The liver showed a slight increase in the connective tissue and a little brown atrophy, but otherwise was normal. As regarded the presence of inflammatory lesions in the calves, Dr. Brooks could not exclude them, but there was no pus and the skin was not reddened except where the blebs had been raised, and here it was deep purple in color. The femoral vessels were palpable and were examined as high as could be reached. Dr. Brooks did not think there was any lesion of the blood vessels which could have been detected by gross examination, and he had not been able to find any lesion microscopically.

---

## A CASE OF SEPTICEMIA, PROBABLY GONOCOCCAL IN ORIGIN.

A. M. PAPPENHEIMER, M.D.

Dr. A. M. Pappenheimer presented a case of septicemia which was probably gonococcal in origin, giving a brief review of the clinical history and post-mortem examination and of the bacteriological findings. The interest of the case lay in the fact that it was a case of general gonococcal septicemia, originating from suppurative salpingitis with the formation of a pelvic abscess,



and unaccompanied by endocarditis or joint lesions. For permission to report the clinical history, he was indebted to Dr. W. E. Studdiford.

The patient was a young colored woman, twenty-three years of age, whose previous history had no bearing on this illness. Three weeks before admission to Bellevue Hospital she had severe pains in her abdomen and noticed a vaginal discharge. This was all the history which was obtained, as the patient was delirious on admission. She was in the hospital from March 3rd to March 25th, and during that time ran a persistent irregular temperature, 101 to 104°, and was constantly delirious. She developed rather marked meningeal symptoms, so much so that meningitis was suspected. The spinal fluid, however, was clear and sterile. A blood culture which was taken shortly after she entered the hospital, was also sterile. Pelvic examination showed the presence of a large mass in the posterior fornix. There was a profuse purulent vaginal discharge, smears from which showed Gram negative diplococci. A gonococcal septicemia was suspected, and from March 16th until she died, she was treated with injections of Dr. Torrey's anti-gonococcus serum. The only effect noted was a slight lowering of the temperature.

The post-mortem examination was interesting chiefly from a negative point of view. An encapsulated abscess containing a few drachms of thick pus was found in the posterior cul-de-sac between the uterus, rectum and right Fallopian tube. There was no general peritonitis. In general, with the exception of the heart, the organs showed nothing but slight parenchymatous changes. The myocardium, on histological examination, showed areas of round-celled infiltration, degenerative changes in the nuclei, and edema. There was no meningitis.

Smears made from the pus of the abscess showed typical gonococci. Unfortunately the abscess cavity was opened before its presence was recognized and the cultures were overgrown by contaminating bacilli.

Smears from the spleen contained a great number of Gram negative diplococci. Some of these were morphologically typical; others were irregular in size and staining, resembling the involution forms of old cultures, and were difficult to identify positively as bacteria. Ascitic agar streak plates were made from the spleen, but only a few extraneous colonies developed.

---

## A CASE OF COMPRESSION PARAPLEGIA.

V. P. GIBNEY, M.D.

Dr. V. P. Gibney presented a case of compression paraplegia directly due to abscess dissecting on the anterior surface of the canal, from Pott's disease of the third and fourth cervical vertebræ.

A colored girl, six years of age, was admitted to the Hospital for the Ruptured and Crippled on January 31, 1907, with a history of enlarged glands in the neck on the right side for over a year. The glands had been removed at the Polyclinic Hospital and found to be tuberculous. Last June, pain in the back of the neck came on with rigidity and distress on walking. Later she was brought to the Out-Patient Department of the Hospital for the Ruptured and Crippled, and a plaster-of-Paris jacket with head spring was applied. About the first of December the lower limbs became weak, and shortly afterwards paralysis of both upper and lower extremities

developed, so that when she was admitted she had paraplegia as well as brachial paraplegia. There was no deformity of the cervical vertebræ, but the spinal column was quite stiff here and the least movement produced pain and distress. So a "Minerva" jacket (see picture) was applied promptly and immediate relief followed. That is, the child was happy, the



fingers in the right hand began to move, and nothing further developed until February 23, when dyspnea with weak and irregular pulse came on. Strychnin was employed with temporary relief, and a large fenestrum was cut out over the front of the jacket; but relief was only temporary, as death supervened on the morning of February 25.

An autopsy made by Dr. Jeffries revealed a pneumonic process of the lower lobes of both lungs and early miliary tuberculosis. An abscess was uncovered on the

anterior surface of the bodies of the three lower cervical and three upper dorsal vertebræ. Its entire extent was not discovered until the column was removed, when it was found that the intervertebral disk between the third and fourth cervical vertebræ was absorbed and the two vertebræ entirely separated. The pus cavity extended into the spinal column and caused pressure over about two inches of the cord. The specimen shown demonstrated this. The cord was not removed for examination.

---

## A CASE OF ACUTE LYMPHATIC LEUKEMIA.

S. O. SABEL, M.D., AND G. R. SATTERLEE, M.D.

Dr. G. R. Satterlee presented a case of acute lymphatic leukemia clinically suggesting a myelogenous origin, which had been studied by Dr. Sabel and himself. Considerable discussion has recently been concerned with the subject of the origin of the leucocytes in leukemia. Probably the chief cause of the unsettled state of opinion lies in the "imperfection and instability of our knowledge of the histogenesis and interrelation of the different forms of leucocytes". Considerable confusion has also arisen over the naming of the cells. At times the clinical features are too striking to be ignored, and this case had been studied from the clinical standpoint principally. Unfortunately there was no autopsy. In regard to the origin of the leucocytes typical of the disease there are two schools of diverse opinions. The first is that of Ehrlich and his followers; the second that of Pappenheim, Grawitz, and others. Ehrlich believes that two forms of leukemia exist: first, the lymphatic,

due to primary disease of the lymph glands; second, the myelogenous, due to primary disease of the bone marrow; and that it is not possible for the disease of one form to change into that of the other form. The second school considers the bone marrow as the birthplace, pathologically, of all cases of leukemia. Numerous cases of lymphatic leukemia with slight or no enlargement of the lymph glands have been reported. The case reported by Dr. Sabel and Dr. Satterlee could be added to this class of cases and might possibly throw some light on the question of the origin of the leucocytes. Because of the absence of a post-mortem examination the changes in the bone marrow could only be inferred by clinical deduction.

The opportunity for studying this case was offered in the service at the Washington Heights Hospital. The patient was thirty years old, male, white, born in the United States, credit man, married, admitted March 20, died March 31, 1907. Clinical diagnosis, acute lymphatic leukemia. The patient was brought to the hospital in the ambulance complaining of weakness and nose bleed. The family history was negative. His father and mother were both living, one aged sixty-six, the other sixty-two. He had six brothers and two sisters, all alive and well. He was born in New York and had always resided here with the exception of eleven years spent in Ohio. He said that his business was a severe tax on his nervous system. His habits were not good. He was always indoors and took little exercise; his meals and sleep were regular. Though he smoked but moderately he averaged one glass of whiskey a day, and had used to drink heavily.

Previous illness: As a child he had measles, mumps, whooping-cough. He denied all other diseases except



malaria; admitted gonorrhea, but denied syphilis. For the past six months he had noticed an increasing frequency of micturition. For the past two months he had been very weak. He had a slight hemorrhage every time he blew his nose. The stools were of normal consistency but were black. The appetite was very fair. Weakness became more marked, and on March 14 a physician was consulted. On March 18, he lost six ounces of blood by epistaxis. During recurring attacks he lost considerable blood. About this time he noticed dark patches on his leg. These were undoubtedly subcutaneous hemorrhages. On the day of admittance into the hospital he had a severe nasal hemorrhage. When first seen by the ambulance surgeon the patient was very restless and when placed in an erect position fainted.

Physical examination, March 21, showed a fairly well nourished man; musculature flabby; appeared weak; eyes protruding, scleræ of a pearly hue, pupils dilated, conjunctivæ blanched. The mucosa was very pale; there were slight hemorrhages from the gums. The nasal cavity showed a blood clot from recent hemorrhage. Of the glands of the neck only one was palpable. This was about the size of a pea and was firm in consistence. All other superficial lymph glands were negative. The tonsils were not enlarged. The thyroid appeared normal. There were several small subcutaneous ecchymotic areas on the left arm and on the back of the hand. There were four or five spots on the leg. The heart was not enlarged; there was a blowing systolic murmur at the apex. The vessel walls showed no sclerosis. Pulse was 84, regular, and easily compressible, and of 130 mm. tension. The lungs showed nothing abnormal. Neither the liver nor the spleen was palpable. The reflexes were exaggerated. There was moderate ankle clonus. Perception

of heat and cold was not very keen. On admission the patient's temperature was 100.4°; respirations, 22. Blood examination showed white cells, 120,000; red blood cells, 1,500,000; hemoglobin, 15 per cent.; index, 0.5. Differential count showed

Polynuclear leucocytes,	9	per cent.
Large lymphocytes,	78	"
Small	9	"
Transitionals,	3	"
Myelocytes,	1	"

There was quite marked poikilocytosis and no nucleated red cells.

The next day the patient was put on iron and arsenic and this medication was continued. Patient felt much better, temperature normal. Blood examination showed practically the same conditions. The urine was amber and alkaline; specific gravity, 1.022; trace of albumin; triple amorphous phosphates, and a few epithelial cells.

Blood examination the next day was practically the same. In fresh drop the red blood cells quickly massed together and this could be distinguished by the unaided eye. Fibrin formation was very rapid; and the individual strands between the red cells were very coarse.

*March 24:* Pallor had become more marked. Blood examination showed white cells, 71,875. Red cells were slightly increased, to 1,720,000; hemoglobin, 15 per cent. Quite marked degeneration of the nuclei and cytoplasm of the leucocytes was noticed.

*March 25:* Very marked constipation. Urine showed specific gravity, 1.015; no albumin; no sugar; large amount of indican; microscopically there were a number of polynuclears and quite a few large lymphocytes.

*March 26:* Pulse, temperature, and respirations

normal. Neither the spleen nor any of the lymphatic glands, with the exception of the one in the cervical region, were palpable.

*March 27:* Gums bled slightly. Patient complained of pain in the head.

*March 28:* Temperature rose to  $101^{\circ}$ ; pulse, 122. Patient complained of extreme soreness of the gums from which there were slight hemorrhages. Thirty to forty ounces of urine were passed in the twenty-four hours. White cells were 25,100; hemoglobin, 20 per cent. (through an error the red cells were not counted). Differential count showed

Polynuclear leucocytes,	12.5	per cent.
Large lymphocytes,	74.0	"
Small " "	4.5	"
Transitionals,	6.0	"
Polynuc. eosinophiles,	1.0	"
Large mono. " "	1.0	"
Myelocytes,	1.0	"

*March 29:* Temperature, 99 to  $101.2^{\circ}$ ; pulse, 108 to 120; respirations, 24. Patient was slightly delirious at times. There were hemorrhages from the nose and gums; he complained of soreness in the thighs. Spleen was palpable, though the enlargement was very slight. Urine was amber, slightly cloudy, flocculent; specific gravity, 1.010; no albumin; no sugar; no indican; polynuclear leucocytes and large lymphocytes. A moderate number of red cells and a few granular casts were found, showing that there were some hemorrhages in the urinary tract. Blood examination showed 44,000 white cells; red cells, 940,000; hemoglobin, 20 per cent.; index, 1.08.

*March 30:* Patient much weaker; he was in a constant condition of delirium and stupor. Gums bled continuously. Face cyanotic. Tenderness over the spleen

and tibia. Patient urinated involuntarily. Temperature 102 to 103.4°; pulse 106 to 120; respirations, 22 to 26.

*March 31:* After a restless night the patient complained of severe thirst; breathing became difficult; and death occurred.

In this case, the blood picture of which was that commonly called acute lymphatic leukemia, the only symptoms were the numerous small hemorrhages, loss of strength, constipation, and appearance of anemia; there was no enlargement of the spleen or lymphatic glands, with the exception of one cervical gland. The patient was under observation eleven days, but not until the ninth day was the spleen palpable or tender; and for the first time evidence of tenderness upon pressure over the tibia and femur was then noted. On the following day there was soreness in the thighs. In the absence of any enlargement of the lymphatic glands, and the very slight though late enlargement of the spleen, the soreness in the thighs and the tenderness over the spleen and long bones which was very marked, suggest that the original lesion productive of the blood changes was located in the bone marrow and the spleen. It was unfortunate that these clinical deductions could not be corroborated by a necropsy.

### *Discussion.*

DR. F. C. WOOD said that in connection with this case of Dr. Satterlee's he would like to bring up a point which had greatly interested him; that is, as to how far one might go in making a diagnosis of lymphatic leukemia from the blood count alone. He had recently seen a number of interesting cases with high relative and absolute lymphocyte counts which were evidently not lymphatic leukemia. These cases all recovered. Some of them

had had syphilis which might have accounted for the lymphocytes and some had general glandular enlargement. All, however, had left the hospital in good condition. He had seen other cases which did not seem to be lymphatic leukemia from the blood, cases in which the lymphocytosis was not very high, although at autopsy lymphatic bone marrow was found. These facts had rather shaken his belief in the possibility of a diagnosis of obscure cases of this type of disease.

DR. E. LIBMAN said he thought that if these cases were regarded as a type of reaction of the bone marrow or other blood forming organs to certain known and unknown infections and intoxications it would be much easier to understand the atypical cases. It was possible to have all kinds of findings in infections, and he thought the safest way would be to say more often that one was dealing with a lymphemic or myelomic picture (and so on), and then try to find out what the picture was due to, or what the lesion was. He had seen a case recently of a girl suffering apparently from influenza. A few days later a gland at one side of the neck enlarged; her temperature was up ( $102^{\circ}$  to  $103^{\circ}$ ); white cells, 8,000, most of which were large mononuclear elements. There were also a few nucleated red cells and neutrophile myelocytes. She shortly developed bone tenderness and a large spleen. After about six weeks she entirely recovered and her blood had been negative ever since. In other words, this was a case with a peculiar reaction of the blood to an infection. In such cases one must be certain that the infection preceded the blood changes. In a case Dr. Libman had seen recently, of apparent hemorrhagic diathesis, in which streptococci were found in the blood, it was found that the infection was secondary (from the throat) to an acute leukemia.



DR. SATTERLEE said he agreed with Dr. Wood in that he thought a great deal hinged on the origin of the leukemia. This blood showed a leukemic picture. The patient had not been seen before and it was impossible to tell whether he had had an infection. A great deal hinged also on what these different cells were called. Some authors call them one thing, and some another. He would classify this case with the leukemias on account of the clinical symptoms, the high leucocyte count (120,000) and the large percentage of the typical large lymphocytes.

---

## A CASE OF SYPHILIS OF THE HEART.

T. C. JANEWAY M.D., AND W. W. WAITE, M.D.

Dr. T. C. Janeway reported a case of syphilis of the heart, the interest in the clinical history hinging on the post-mortem finding of a rather rare lesion. The patient was a strong Irish laborer, forty years of age. He had had syphilis at nineteen and had suffered from rheumatic pains ever since. He entered the hospital having had shortness of breath for some months particularly at night. There were typical signs of aortic insufficiency. There was a marked collapsing pulse and a large range of pulse pressure. The history was a straightforward one of a rather badly treated syphilis. A diagnosis of syphilitic aortitis with aortic insufficiency was made. The absence of any systolic murmur and of any noticeable diminution in the suddenness of the pulse was rather striking in view of the autopsy. This showed a marked aortic stenosis with absence of any of the clinical signs in addition to moderate aortic leakage. The ex-

planation of the absence of murmur was obvious; the aorta was not narrowed at any one point, but for a considerable distance; therefore there was no chance for the production of abnormal currents beyond the point of contraction. The man was in the wards for ten days, complaining only of inability to lie down without dyspnea. A few days before death there was a small effusion in the chest, then suddenly he developed edema of the lungs and died inside of five minutes.

Dr. W. W. Waite demonstrated the autopsy findings in this case. The important finding was in the heart. On opening the thorax there was a large excess of fluid in both pleural cavities and in the pericardial cavity. The upper portion of the pericardial cavity was obliterated and the aorta and pulmonary artery were firmly bound together. On removing the heart it was found considerably enlarged, weighing 515 grams. On section, the right side was free and the valves were in good shape. The pulmonary artery was free, and the surface of the intima was of a peculiar glairy appearance and of a pale pinkish color, due to numerous fine vessels present in the deeper substance. In the heart muscle, directly beneath the right pulmonary segment, there was a small, white, well defined patch, about four mm. in diameter, which extended into the heart substance. Most of this was removed for microscopical examination. The left auricle was free. The segments of the mitral valve were slightly thickened along the line of closure. The wall of the ventricle was thickened, the trabeculæ coarse, and the cavity larger than normal. On section, the wall of the base of the aorta was found markedly thickened with distinct puckering of the intima and a narrowing of the lumen. The remarkable thing was that the ascending aorta was completely surrounded by a

dense, firm, white, semi-translucent, very elastic-like tissue. This increase of connective tissue partly surrounded the pulmonary artery and extended to the arch and about the vessels arising from it. The aortic segments were slightly thickened. At the junction of the right and posterior cusps there was a large and deep ulcerating area. The edges of the ulcer were raised and thickened. No sections were made of this area, but it was considered as a broken-down gumma.

Microscopical examination showed that the nodule in the heart muscle was a gumma with a large amount of connective tissue, fibrous cells, small round cells, and many giant cells. No tubercle bacilli could be found. A section of the firm fibrous tissue about the aorta showed much the same picture, except that there were fewer giant cells and more connective tissue of a hyalin nature. In the more recent deposits there were numerous small round cells of the lymphoid type. The small vessels in the intima and media were dilated and filled with blood. The intima itself was greatly thickened, and necrotic, and showed hyalin degeneration. On the descending aorta there was nothing but patchy sclerosis. The lymph glands were enlarged and pinkish in color. There was some hypertrophy of the lymphoid tissue. The heart muscle itself was fairly well preserved, showing some chronic interstitial myocarditis with hypertrophy. There was also a small gumma on the surface of the liver.

### *Discussion.*

DR. HORST OERTEL said that while he did not wish to enter into any discussion of the histogenesis of gummata, there were one or two points in the specimens which he had examined under the microscope to which

he would like to call attention. The first was the occurrence of a very large number of giant cells in the sections from the gumma of the heart muscle. The discussion as to the occurrence of giant cells in gummata had been recently revived, and some authors had taken the stand that these cells do not occur unless the gumma is complicated with tuberculosis. This case showed a large number of giant cells, and careful examination showed nothing to indicate the presence of tuberculosis. Second, as to the origin of giant cells; some have thought that all giant cells were transverse sections of thrombosed vessels. The sections under the microscope showed very plainly that nothing of that kind existed here, but that they probably resulted from fusion or overgrowth of granulomatous cells. Another point was the presence of a very large number of eosinophiles. Dr. Oertel had not seen these very frequently in gummata and had been very much struck by their appearance in this case in the sections from the heart muscle.

---

## SPECIMEN SHOWING RARE SEQUELÆ OF INTUBATION.

BINFORD THRONE, M.D.

One of the rarest complications of intubation is the development of a pretracheal abscess. I have seen this once at the Kingston Avenue hospital since the first of July, 1906. During this time we had about one hundred and fifty intubation cases. At the Willard Parker Hospital I saw three cases. Of these three, one was in a series of cases of which I kept careful records. Of these, one hundred and fifty-two were intubation cases.

The following is a short clinical history of these three cases:

*Case 1:* N. C., aged four years; seven days illness; admitted on October 4; intubated before admission. Abscess developed on the twenty-first day after intubation. The case was intubated thirteen times before the opening of the abscess. It was extubated three times; and the tube was coughed up nine times. The abscess was a soft mass about two inches in diameter situated in the median line of the neck below the larynx and just above the isthmus of the thyroid. It developed very rapidly, was opened on October 25, when about one and one-half ounces of pus discharged. There was no communication with the larynx. The cervical glands were involved secondarily, and those on the right side were incised on November 1.

*Case 2:* J. S., aged fifteen months; eight days illness; admitted October 11, 1904; intubated before admission. The case was intubated eight times before the formation of the abscess. It was extubated three times; and the tube was coughed up four times before the opening of the abscess. The tube was coughed up twice after the abscess was drained and the case was extubated once. The abscess was opened on the eleventh day after the first intubation.

*Case 3:* G. B., aged three years and nine months; two days illness; intubated before admission; admitted on March 9, 1905. The abscess was first noticed on March 20, and opened on March 21. The abscess was opened on the fourteenth day after the first intubation. The case was intubated four times before and eight times after the abscess was formed.

All of the above cases recovered and were discharged.



The patient from whom the specimen presented was taken was admitted to the Kingston Avenue Hospital on March 5, 1907. This patient was three years and one month old, and was admitted with the following history. Patient had been intubated twenty-one days previously, was extubated once, and re-intubated some time during the interval between the first intubation and the day prior to admission to the hospital. The history was that the physician who had intubated the child had tried to extubate on March 4, and again on March 5, both times unsuccessfully. Upon admission the patient was suffering from extreme dyspnea. On examining the larynx no tube could be found. A 4-5 year rubber tube was carefully and slowly inserted into the larynx and this tube at no time struck any foreign body. Introduction of this tube relieved the dyspnea somewhat. Physical examination of the child showed exaggerated breathing, tubular in character over the right lung, and greatly diminished respiratory murmur and no expansion on the left side of the thorax. A diagnosis of occlusion of the left bronchus by an intubation tube which had been pushed through the larynx was made. The condition of the child was so grave that an operation to remove this tube was not considered justifiable. A pretracheal abscess which had been opened before admission was present. The duration of this was not known. On March 8, marked emphysema of the subcutaneous tissues of the right side of the neck extending down over the upper part of the chest to the second rib was present. The child died on March 9.

Permission having been obtained, the larynx, trachea and bronchi were removed. In the lower part of the larynx extending into the left bronchus a three year rubber intubation tube was found. The head of this tube

was about one-half inch below the lower end of the 4-5 year rubber tube which had been inserted on admission. Upon the anterior wall of the trachea and a little to the right of the median line, where the lower end of the intubation tube came into contact with it, there was an ulcerated area, about 1-32 of an inch in diameter, extending entirely through the wall of the trachea. In the larynx the vocal cords were entirely gone. An ulceration was present on either side of the median line, extending through the cricothyroid membrane, about 1-16 of an inch in diameter. Ulcerations were also seen at the base of the epiglottis and on the aryepiglottic folds. The cricoid cartilage was intact. Lying upon the anterior wall of the trachea, above the isthmus of the thyroid and just above the origin of the inferior constrictor of the larynx, was a small lymph node. This lymph node drained the upper part of the trachea and the lower part of the larynx, and it was at this site that the first swelling was seen.

The specimen showed three points of interest: First, ulceration of the larynx extending through the cricothyroid membrane. This was the starting point of the infection which caused the pretracheal abscess. Second, ulceration extending through the trachea where the lower end of the tube had been in contact with it. This was the starting point of the emphysema. Third, an intubation tube pushed through the larynx into the trachea and bronchus without rupture of the cricoid cartilage.

---

## A CASE OF BILATERAL SUPERNUMERARY INDEX FINGER REPLACING THE THUMB.

L. T. LE WALD, M.D.

Dr. L. T. Le Wald presented a case of bilateral supernumerary index finger replacing the thumb which he wished to put on record. One frequently saw supernumerary fingers which were rudimentary affairs, but in the case presented the thumb had three phalanges and resembled a finger, and more closely resembled the index finger. The X-ray photograph had brought out not only the additional phalanx but certain other points which tended to show that this in its development was a finger rather than a thumb. The patient was a man of twenty-eight years of age, born in Virginia. The deformity was not present in any other member of the family; one of his brothers had double jointed wrists. The case had come to notice on examination for enlistment in the army. Prof. Huntington, of Columbia University, had been consulted and had stated that in a large number of dissections this deformity had never come under his observation. On searching the literature, however, Dr. Le Wald had found a case reported by Annandale in 1864. In Annandale's case the hand was perfectly developed in every way except that the thumb was like a long forefinger, having three phalanges. The patient was a girl who was otherwise well formed. The deformity in Annandale's case was apparently unilateral. In the present case the thumb showed the peculiarity in both hands. The palmar surface of the thumb instead of being shallow was more rounded out, like that of a finger. The last joint was slightly flexed instead of being extended. The first metacarpal was nearly twice as

long as in a normal thumb and resembled that in a finger. Instead of classing this deformity as a case of supernumerary phalanx in the thumb, Dr. Le Wald thought it might be better to consider it as a replacement of this member by a finger.

---

## THE PRESENCE OF AMEBÆ IN THE MOUTHS OF HEALTHY INDIVIDUALS.

L. T. LE WALD, M.D.

Dr. L. T. Le Wald presented a preliminary report of investigations which he had been carrying on as to the occurrence of amebæ in the mouths of healthy individuals. The subject had been brought forward because there seemed to be a great deal of question as to the constancy of this organism in the mouth. It has been reported in pathological conditions in the mouth and upper respiratory tract. In Delafield and Prudden's Pathology it is stated that species of ameba have been found parasitic in the human mouth, intestine, and bladder. Braun, in his book on animal parasites in man, which is probably the most complete work one can consult, states that *Ameba gingivalis*, *buccalis*, and *dentalis* have been reported in the mouth. Of these three species Braun thinks the last one may be disregarded as its discoverer has himself suggested the possibility of his having mistaken salivary corpuscles for amebæ. The other species have been found on the tartar of teeth.

Dr. Le Wald had taken up this study some time ago while in the tropics. The first examination showed amebæ which looked like *Ameba coli*. Of the following

cases some showed amebæ and some did not. Dr. Le Wald then began a systematic study of scrapings from the mouth for amebæ, and made a considerable number of observations while still in the tropics. In a series of scrapings from the mouths of Filipinos, for instance, there were fifteen positive and four negative. He had carried on these observations in the United States by using a warm stage so as to simulate tropical conditions, and had been able to convince himself at once that these amebæ could be demonstrated in the mouth almost constantly, no matter how much care was taken of the teeth. In the first examination of 100 cases he had obtained positive results in 71. In going over some of the negative cases and making repeated examinations he had found amebæ in four more; and he felt that with repeated examinations they could be demonstrated in most, if not all, of the other cases.

The morphology of these organisms had not been worked out completely, and he hoped to undertake some investigations to demonstrate what the correct designation of this organism should be. He considered it probably identical with the *gingivalis* and *buccalis*, and would suggest that one of these names be retained or the organism called *Ameba oralis hominis* which would indicate its constant presence in man.

The technique was not very simple. If one merely took saliva from the mouth, or even tartar from the teeth, he would not find the organism. It was necessary to go a little deeper and scrape away the tartar and work a sterilized platinum loop under the gum, bringing away a sort of translucent gelatinous material. This should be put at once on a slide on a warm stage. If the material was very thick a little saliva should be added, and the specimen then covered with a cover glass. The organ-



ism was from 10 to 20 micra in diameter. It was always possible to distinguish it on a warm stage by its motility. There could be no question of confusing it with epithelial cells or with leucocytes which are commonly present in large numbers.

Dr. Le Wald had examined persons coming from all parts of the country and from abroad, and the constancy with which the organism had been found left no doubt in his mind as to its presence in the human mouth in health, equalling in this respect the presence, for instance, of the *B. coli communis* in the intestine.

Active amebæ were exhibited under the microscope.

---

## EXPERIMENTAL BLASTOMYCOTIC LESIONS.

HANS ZINSSER, M.D.

It would be a needless waste of time to introduce my communication by a review of the literature upon pathogenic blastomycetes. This, since Busse's paper in 1894, has accumulated until it is now quite formidable; and, furthermore, it has been very thoroughly collected in the papers of Ricketts, Gilchrist, Hektoen, and others.

The organisms with which it has been my privilege to do a few simple experiments were cultivated from a case in the care of Prof. Brewer, the clinical details of which were reported at the last meeting of this Society.

The first cultures were made from the pus as discharged from the abscess, which, morphologically, contained besides the organisms in question, a Gram-positive coccus which did not appear in the cultures after incubation. This apparent inhibitory effect on the other

organism is in contrast to Hektoen's case, where it was difficult to separate the organism from a pseudodiphtheria bacillus, but agrees with the experience of Gilchrist and Stokes.

There was no difficulty about cultivation, small, raised, punctate colonies appearing after about forty-eight hours on glycerin-agar slants. Morphologically, the organisms show the following characteristics:

They are almost uniformly round; isolated, slightly oblong forms are occasionally seen in old cultures. They vary much in size, ranging from that of a blood platelet to two or three times that of a red blood cell. They are composed of a definite cell membrane which appears doubly contoured and quite thick. About this, in the first cultures out of the subject and in the tissues of animals, there appears an envelope resembling the capsule of some bacteria. This has disappeared in old cultures and more recent transplants. Within the cell membrane the protoplasm, in unstained hanging-drop preparations, appears granular and is vacuolated. The granules occasionally exhibit Brownian movements, and are highly refractive. The organisms take all the usual aniline dyes easily, and are, by the usual methods, invariably overstained so that little or no structure can be made out. Structures can be made out in fixed smears with Giemsa, Wright's, Jenner's, the eosin-azure stain of Prof. Wood, and aqueous thionin; but are difficult of interpretation. There are usually one or two larger eccentrically placed bodies taking the nuclear stain about which lie numerous smaller granulations which are equally distributed throughout the protoplasm. Often the larger bodies, when encapsulated, assume a crescentic form. Whether these are degeneration phenomena or not, I was unable to determine. On agar

these organisms grow easily, producing in forty-eight hours at 37° C., a small colony the structure of which is not unlike that of a staphylococcus colony. On agar streaks they grow to only a slight depth, but actively on the surface, heaping up in a deep, yellowish creamy growth. On potato, heavy and whiter. On litmus milk, growth, no change. On gelatin, no liquefaction; but this is due possibly to the almost imperceptible growth at room temperature.

Unlike most forms described, they grow, at present, very poorly on all fluid media and to this may be due the absence of fermentation in dextrose, lactose and saccharose Smith tubes, and in dextrose, lactose, galactose, maltose, mannit, saccharose, levulose, and dextrin tubes of the Hiss serum waters. The slow but definite increase, however, which this organism has already shown in its powers of growth on artificial media, during the comparatively short period of observation, makes it not unlikely that the sugar fermentations may still take place when growth on fluid media becomes more active; and with this in view the experiments will, of course, be repeated after a few months have elapsed.

Reproduction is by budding, and in no case, even in the agar and gelatin hanging-drops, have mycelia been observed. In old cultures daughter cells grow and bud again without detachment from the mother cell, thus forming strings of organisms. Again, they may separate from each other by a short distance, yet remain connected by a thin, straight, bridge-like line, which takes the stain of the protoplasm. I have observed a single bud while detaching from the mother cell off and on during a period of forty-eight hours at room temperature, and seen only an almost imperceptible change in size of the bud. Multiplication, therefore, at this temperature can be only extremely slow.

The question of the classification of these organisms is not a simple one. The blastomycetes or *Torulæ* as a class, especially those which produce mycelia, are closely related to the Hyphomycetes; but not falling in without variation with any of the accepted classes, they have been shelved by botanists, and put, as Klöcker has expressed it, into a "Rumpelkammer" together with other forms that can not be properly placed, under the head of the "Fungi Imperfecti". Others, like Gottschlich, separate them entirely from the Hyphomycetes, and with the true yeasts or Saccharomycetes, put them under the heading of "Sprosspilze" or budding forms. In view, however, of the many transitional forms described, some of which form mycelia late or irregularly, like that of Hektoen, it does not seem that an absolute separation can be made. As to attempts at separating these forms among themselves, this seems to have been still more confusing. Casagrandi after an exhaustive attempt declares a morphological differentiation impossible. Ricketts, Weis and others have made careful comparative biological studies. Few of the forms described seem to correspond in all details. The forms under consideration seem closest to the ones described by San Felice, cultivated from adenocarcinoma, and those of Plimmer and Klein, in that they do not form mycelia, and have not, so far, fermented sugars, nor formed spores. Inasmuch, however, as Hansen, the greatest authority on yeasts, has been able materially to change forms of yeast fungi by cultivation, it does not seem justifiable after my short acquaintance with these organisms to attempt to assign them a place.

With salt solution emulsions of the organisms, five guinea-pigs, a rabbit, and a gray mouse were inoculated. The mouse, which received an enormous dose subcuta-

neously, died in forty-eight hours, and the organisms could be recovered from the heart's blood. The rabbit, inoculated intrepleurally, after three weeks began to emaciate, to lose hair, and to appear so ill that death was expected. After about ten days, it recovered and when killed, five weeks after inoculation, no lesions could be found.

Four of the guinea-pigs were killed after from four to seven weeks, none of them appearing very ill at the time. In all of them, however, lesions were found which were so similar that a single description will suffice for all. Two of the pigs inoculated intrapleurally and one intraperitoneally, showed the lesions only in the lungs and spleen, no lesions being found at the point of inoculation and both lungs being always affected. The pleura and the peritoneum in these cases were clear.

One pig inoculated subcutaneously into the abdominal wall showed lesions in the lymph nodes below the point of inoculation and two small nodules in the right lung. The fifth pig was not killed, but, after nine weeks, was found dead without apparent previous illness. This animal again showed lesions in the spleen and lungs, and also in both kidneys. It is interesting to note that this last animal was pregnant at the time of death and that no lesions could be found in either the embryos or the placenta.

Microscopically the lesions obtained have roughly the appearance of fresh miliary tubercles. They range in size from very minute points to the size of a pinhead. In the lungs they are usually close together, and where they are very numerous portions of the lung appear anemic in color and like infarcts; but microscopically this seems to have been due rather to collapse of the alveoli—areas of atelectasis. The lesions in the ab-



dominal lymph nodes of one of the animals above mentioned were extensive, and the nodes were as large as small hazel nuts, and extremely hard. These lesions were shown to consist chiefly of solid masses of organisms lying in a reticulum of connective tissue with remnants of lymphoid tissue chiefly along the periphery.

Microscopically the lesions are much alike, differing only somewhat with each organ, and corresponding in most essentials to those observed by others. In the lungs the nodules consist, in the pigs killed after four to five weeks, of a central area composed of parasites of varying size, some of them budding and some of them retaining their extraneous capsule. Between the parasites pass thin fibrils of connective tissue, in the meshes of which there is often deposited a granular mass of detritus resembling the products of coagulation necrosis as seen in tubercles. Immediately about this there are numerous young connective tissue cells, large, swollen, epithelial cells in the half destroyed alveoli. In other lesions many cells resembling the epithelioid cells of young tubercles are present. Occasionally an acidophilic cell is seen. About such nodules there is an area of extreme congestion with swelling of the alveolar epithelium and red blood cells and leucocytes in the alveoli, forming small, broncho-pneumonia-like areas, except that polynuclear leucocytic invasion is markedly slight. It is noticeable that giant cell formation is much less active in the lungs than in the other tissues involved—an observation made previously by Gilchrist.

In those that have lived a few weeks longer the area of congestion has disappeared (Pig II, lung). A firmer connective tissue capsule surrounds a clear area in which organisms, now chiefly encapsulated, lie in clear spaces,

separated by denser connective tissue partitions. In these cases some giant cell formation is visible.

In the spleen, in those animals in which resistance was still high, the histological picture is a striking one. The organisms lie in small groups, immediately surrounded by clear spaces where the tissue elements seem to have been destroyed. Necrotic cell remnants lie scattered here and there between them. The connective tissue strands which pass between the pairs and triplets of blastomycetes seem not more profuse than could be accounted for by the undestroyed normal tissue reticulum. Immediately about the periphery of the nodules, however, there is a striking formation of giant cells. These form in crescentic fronts about the single parasites and in some cases have completely enveloped them. Immediately about this is a very densely cellular area consisting chiefly of young connective tissue cells. There is very little leucocytic invasion and very little congestion. The most interesting picture of these lesions are the giant cells. These appear to be phagocytic and conform in a general way to the appearance of foreign body giant cells. Wells, and others who have worked with skin lesions, have expressed the opinion that the giant cells about the blastomycetic lesions were of epithelial origin. It is difficult to pronounce upon the origin of such complicated elements, but in part, certainly, the giant cells in our cases are strongly suggestive of fixed tissue cells, both in the form of the nuclei and in the general cell type. The question also of whether these giant cells are formed by nuclear splitting or by coalescence of cells is suggested by places which could be found in which the protoplasm of the doubly-nucleated mass was, in part, separated; and where joined, a distinct division appeared between the parts. This might be interpreted as a junc-

tion or a separation, and, indeed, the giant cell studies of Hektoen tend to show that giant cells can separate into living single elements when their work is done. But since here we are dealing with a still active process, it seems more logical to interpret these pictures as a fusion.

In pigs in which the resistance seems to have been low (Fig 5, which died), and where the organ is more generally riddled with organisms, there is little giant cell formation and very little tissue reaction of any kind in the spleen. There is much tissue necrosis between and about the lesions, and some congestion; but apart from this tissue destruction and replacement by parasites, there is little change. This is also the case in the lymph nodes of Fig 3, where the masses are almost entirely made up of parasites, necrotic tissue and reticular fibrous tissue. In cases, however, where the animal was killed while apparently well and the resistance high, giant cell formation was invariably greater.

In the lesions in the kidneys of Fig 5, the tissue reaction to the disturbing elements is strikingly absent. The small masses of parasites have destroyed tubules and parenchymatous elements in the spaces in which they lie, nothing remaining but the connective tissue framework of the organ, perhaps slightly increased and thickened. About this the nodules abut almost directly upon only slightly changed kidney tubules. Throughout all the lesions it is noticeable that the damage done is chiefly mechanical and that toxic effects upon the neighboring cells are extremely slight, if present at all.

#### *Discussion.*

Dr. JAMES EWING said that at the last meeting of the Society he had attempted to discuss this organism

without having seen cultures of it, and it seemed necessary for him to say now that he thought there was no clear relationship between this organism and the one isolated from a case in the service of Dr. Coley. The latter organism formed abundant mycelia, grew at room temperature or even in the ice box, and had cultural and pathogenic characteristics quite distinct from this organism.

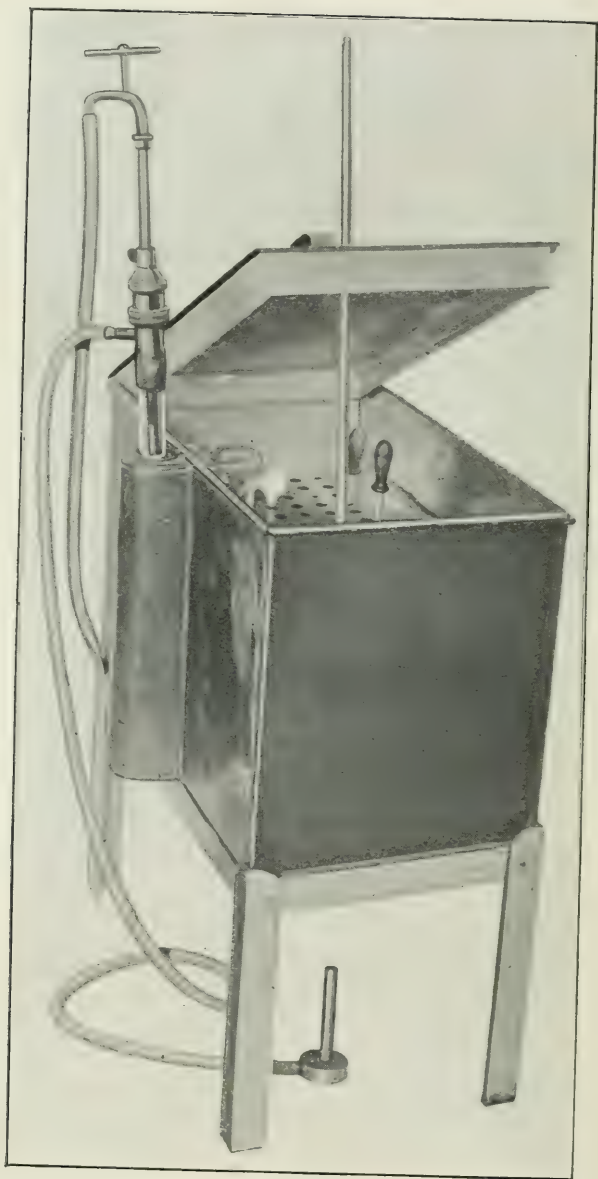
Dr. ZINSSER said that another case had come recently to his notice, occurring in St. Luke's Hospital. This was a case of abscess of the abdominal wall from which cultures were made. These showed the presence of yeast, which had definite morphological characters and showed budding. With this appeared a bacillus which stained with Gram and which he had not as yet been able to cultivate apart from the yeast.

---

## A NEW AND CONVENIENT DESK BATH DE- VISED FOR INCUBATION AT CONSTANT TEMPERATURES IN OPSONIC WORK.

A. WADSWORTH, M.D.

Dr. A. Wadsworth showed a new form of hot water bath which he had devised to run at a constant temperature, and had found very useful as an incubator in opsonic work. It was composed of two copper boxes, an inner fitting closely into an outer box which were supported by an iron stand, 8 inches high. The outer box was 14 inches long, 8 inches wide, and 9 inches high. The sides up to the level of the water, 6 inches from the bottom and 3 inches from the top, were made double



BATH FOR OPSONIC WORK.

About One-fourth Size.

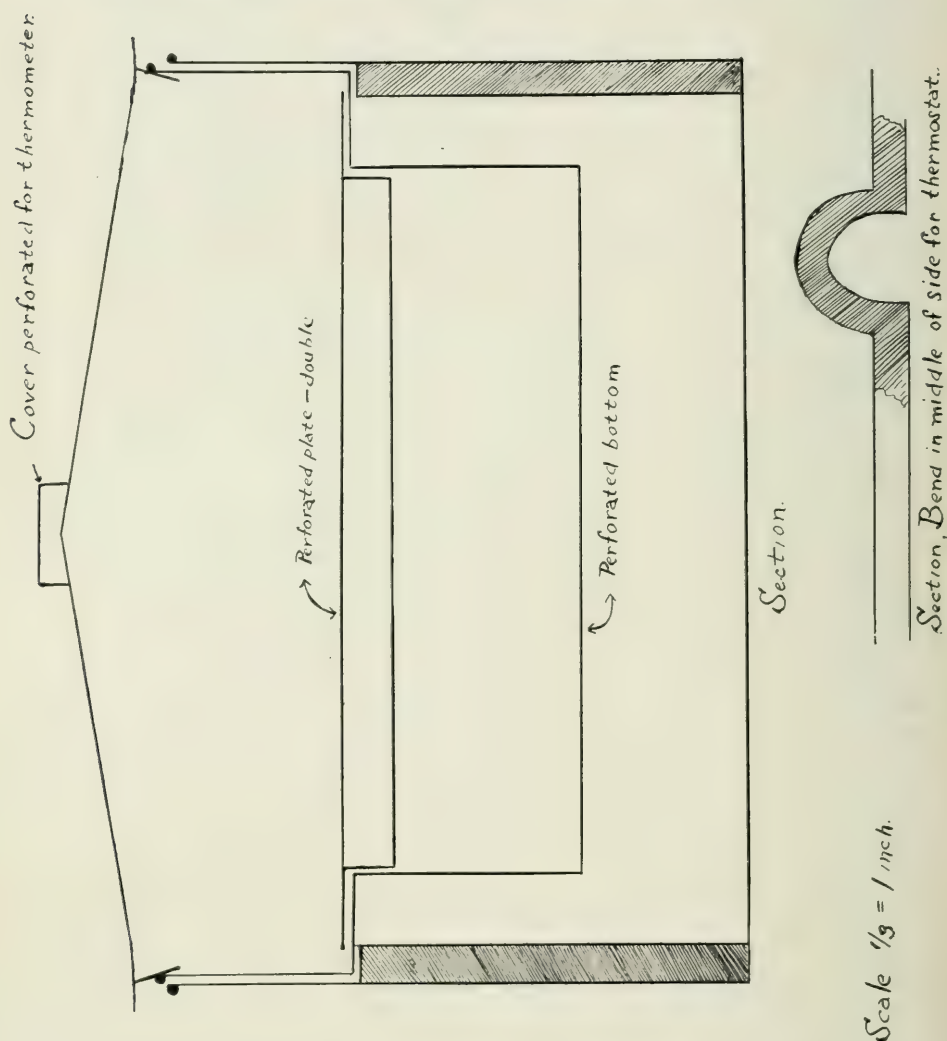


walled, and the space packed with asbestos to prevent too rapid loss of heat. A shelf,  $\frac{1}{2}$  inch wide, was thus formed inside the box at the level of the water. On this rested the inner box, the walls of which, 3 inches from the top, were bent inward  $1\frac{1}{2}$  inches horizontally to form the lower submerged part of this box,  $11 \times 5 \times 4$  inches, thus making a water jacket of  $1\frac{1}{2}$  inches at the sides and 2 inches below. The bottom of the inner box was perforated at regular intervals, the holes being  $\frac{3}{16}$  inches, to allow quick convection and the passage of the capillary tubes used in opsonic work. On the broad shelf of the inner box rested a double plate, also perforated at regular intervals, with larger holes opposite those in the bottom. The size of these holes may be accommodated to the tubes used in the experiments. In this instance they were  $\frac{3}{8}$  of an inch in diameter.

When greater depth to the bath was desired the inner box was lifted and supported on two brass strips. These were bent downward an inch at a right angle to fit across the top of the outer box at the ends, thereby increasing the depth of the bath three inches, or they were placed on the  $\frac{1}{2}$  inch shelf of the long side of the outer box to give an intermediate elevation. However, these procedures were rarely necessary as the bath could be used with the cover off, and the sealing of the water jacket was more complete when the inner box rested on the shelf.

To make a place for the thermoregulator, the wall of the outer box was bent outward  $1\frac{1}{4}$  inches at the middle of the long side. Dr. Wadsworth used a mercury regulator carefully adjusted with alcohol and ether to secure the most delicate control for such temperatures as were required in his experiments. This offset, to a large extent, changes occurring in the gas pressure and proved

to be a useful precaution. Fluctuations in temperature were further controlled by a thin iron plate placed across the stand just above the flame, distributing the heat



over the bottom of the bath. A cover was also made to fit the top of the boxes in any of the arrangements above described. This cover was perforated for a thermometer.

Dr. Wadsworth used thermometers of special construction; some 12, others 18 inches long. They were graduated to read in tenths between  $30^{\circ}$  and  $45^{\circ}$  C., with a maximum error of  $.05^{\circ}$  C.

Such a hot water bath may be set upon a laboratory desk, close at hand, and maintained at any desired temperature with comparatively little fluctuation. Over long periods of observation variations of  $0.3^{\circ}$  C. were noted, but in experiments of a few hours duration this was exceptional. The exposure, in this water bath, of cultures, of opsonic or other tests, proved to be far more reliable than in the air incubators, which often varied greatly during the exposure and at different times.

In Dr. Wadsworth's experience the bath had proved to be a convenient and extremely valuable accessory to experimental laboratory work, not only in the routine opsonic tests but, especially, when accurate determinations were desired of the opsonic, agglutinative, and lytic activity of sera, or of the growth and thermal death point of micro-organisms at different temperatures, and also for pasteurization.

---



# Proceedings of the New York Pathological Society.

---

NEW SERIES, Vol. VII.      October, 1907, to January, 1908.      Nos. 5 to 8

---

## TABLE OF CONTENTS

WOOD, Decidual Reaction in Ectopic Pregnancy.—SCHULTZE, Case of Traumatic Rupture of the Cardiac Orifice of the Esophagus, probably caused by Violent Vomiting.—LIBMAN and CELLER, Case of Chronic Suppurative Lymphadenitis and Pylephlebitis.—PAPPENHEIMER, Case of Typhoid Fever in an Infant: Case of Generalized Infection in an Infant with a Bacillus of the Paratyphoid Group: Case of Universal Fetal Hydrops.—WARD, Case of Diffuse Bilateral Hypertrophy of the Female Breasts.—ZINSSER, Mid-Winter Epidemic of Dysentery of the Hiss-Russell Type: Case of Peritoneal Infection by *B. typhosus* without Intestinal Perforation.—EWING, Note on Involution Forms of *Spirochæta pallida* in Gummata.—SATTERLEE, Case of Hypernephroma of the Adrenal Gland: Case of Angiosarcoma of the Foot: Case of Pernicious Malaria with Autopsy.—BROOKS, Case of Arteriosclerosis of the Pulmonary Vessels.—LEVIN, Reactive Power of the White Rat to Tissue Implantation.—OPIE, Influence of Injected Leucocytes upon the Development of a Tuberculous Lesion.—LEVENE, Leucocytes in Protein Absorption.—NOGUCHI, Sporulation of the Group of *Bacillus aerogenes capsulatus*.—CARREL, Acute Calcification of the Arteries in a Cat with Transplanted Kidneys.—JOBLING, Metaplasia and Lymphatic Metastasis of a Rat Tumor.—JOSEPH, Ratio between the Weight of the Heart and the Weight of the Body in Animals.—FLEXNER, Demonstration of *Treponema pallidum*.—TERRY, Demonstration of the Spirillum of Tick Fever.—WEIL, Case of Tuberculosis of the Ductus Thoracicus.—SCHULTZE, Case of Ureteritis Cystica.—FLOURNOY, Case of Diphtheritic Laryngitis, Tracheitis and Bronchitis.—LEVIN, Case of Endarteritis Obliterans.

---

DR. CHARLES NORRIS, *President.*



## DECIDUAL REACTION IN ECTOPIC PREGNANCY.

F. C. WOOD, M.D.

I wish to demonstrate to the members of the Society two early cases of ectopic pregnancy which are of interest chiefly because of the fact that neither specimen was over two months, and that they show an unusually interesting series of lesions in the walls of the tubes and the vessels.

The first case is that of a young woman, about twenty-five years old. The tubal pregnancy was her second: she had previously been delivered of a healthy child. According to her history the pregnancy could not have existed for more than a month and a half. She had the usual symptoms of pain and collapse, and was operated on at St. Luke's Hospital. The tube, as you see, is an irregular mass, about 7 cm. in length and 3 cm. in diameter. It is covered with a shaggy layer of blood clot and fibrin. The tube has ruptured, and from this rupture has escaped the small amount of blood which was found in the pelvis at the time of operation. Sections of the wall of the tube show that it is edematous and in many places necrotic. This necrosis extends for a considerable distance on either side of the rupture. No fetus could be demonstrated. Besides the necrosis, the wall of the tube is very edematous and is infiltrated with small round cells, chiefly of the plasma type. The outer surface shows no peritoneal endothelium under the layers of blood clot. The vessels are distended with blood, and at one portion of the tube there is a large vein, the wall of which is lined with swollen cells with large darkly staining nuclei. The lumen of the vessel still contains a considerable quantity of blood and a few cells of the type just described. The endothelium is intact on the side of the vessel furthest from the lumen of the tube, the cellular invasion taking place

at the side nearest the tube. There is also a large venous sinus near the vessel mentioned, which contains a chorionic villus. The contents of the tube is chiefly blood clot, though there is at the site of implantation of the fetus a large collection of cells of the trophoblastic type, mixed with masses of syncytium and a few fairly well preserved chorionic villi.

The second case was that of a woman of about thirty-five years of age, who had never had any children. About a month before her admission to the hospital she became pregnant. The day before admission she had some pain in the abdomen, and when examined in the hospital was found to have a mass in the right tube which was supposed to be a salpingitis. The mass was removed by laparotomy and was found to be an extremely early ectopic, with a small tear in the tube just above the broad ligament; but not more than a few c. c. of blood had escaped. The tube is slightly smaller than the previous one, and the walls are thinner. They are edematous and infiltrated. The mucous membrane of the tube is well preserved, except at the site of implantation of the egg. Just below the site of implantation is a venous sinus containing chorionic villi with decidual-like cells; and a short distance beyond this is a large artery, the lumen of which is almost completely filled by decidua, as is well shown in the photograph. A few blood corpuscles still remain in the cells. There are a large number of these decidual-like cells in the connective tissue about the vessel. There are no other abnormalities.

These two cases illustrate a condition about which there has been much discussion in the past few years, and may perhaps explain the early rupture in these cases of ectopic pregnancy. Tubes of this size do not rupture on account of pressure due to the fetus or to the collection of blood, because much larger tubes are seen in pyo- or hematosalpinx. There must be some reason for the necrosis of the wall,

and possibly this infiltration and erosion of the tissues by these decidual-like cells and the filling of the vessels by thrombi composed of these cells may cause a necrosis and sloughing of the wall, which permits of the early escape of the embryo. Whether these cells are true decidual cells, such as are found in the endometrium during pregnancy, is not yet definitely settled; but the general opinion at present seems to be that they are not true decidua, but ectoblastic cells from the embryo which grow down into the tissues after the ovum has penetrated the epithelium at some portion of the periphery of the tube. True decidual cells are sometimes seen in the tube during an intra-uterine pregnancy, or in the opposite tube in the case of tubal pregnancy, or in portions of a tube at some distance from the ovum in a tubal pregnancy; but such formation of true decidua is limited and never assumes as extensive a growth as these trophoblastic cells.

In the two tubes shown there was no evidence of the formation of true decidua in the mucous membrane.

#### A CASE OF TRAUMATIC RUPTURE OF THE CARDIAC ORIFICE OF THE ESOPHAGUS, PROBABLY CAUSED BY VIOLENT VOMITING.

OTTO H. SCHULTZE, M.D.

The specimen in this case had been opened along the median line posteriorly, and presented a rupture of the cardiac orifice of the esophagus, which measured two inches in length in the fresh state. The margins were perfectly clean, gaping about one-half inch, and at each end meeting in an acute angle, thus resembling a fresh wound. The left

pleural cavity was filled with about two quarts of blood discolored by gastric contents. There was considerable cellular emphysema of the mediastinum and neck.

The history of the case was very meager. It was simply that the patient had had intense pain in the epigastrium, had vomited considerable blood and had had all the symptoms of acute anemia. He was infused and an exploratory laparotomy was done, but nothing was found. The case was evidently one of chronic alcoholism, with fatty infiltration of the liver and chronic nephritis. The etiological factor in the lesion was probably violent vomiting.

So far as the cases in the literature were concerned it seemed pretty well established that a normal esophagus may be lacerated in this way. It is not absolutely necessary that the esophagus should be diseased, though, of course, if it is, such rupture might more easily occur. The most common site of rupture is at the lower end. Of the two cases which were presented last year, one was at the cardiac end of the esophagus; in the other case there were two lacerations at the level of the cricoid cartilage. The patient in this case was forty-two years of age. All three cases presented practically the same features, death due to hemorrhage, in this case through complete laceration of the wall of the esophagus communicating with the left pleural sac.

---

## A CASE OF CHRONIC SUPPURATIVE LYMPHADENITIS AND PYLEPHLEBITIS.

E. LIBMAN, M.D., AND H. L. CELLER, M.D.

The case which we wish to present is of more interest from the pathological than from the clinical side, because the patient arrived at the hospital only a few days before death and because she was a Pole from whom a definite his-

tory could not be obtained. The facts, as far as we could obtain them from the relatives and from the various hospitals in which she had been taken care of, were as follows:

She was operated upon on December 1, 1904, at the J. Hood Wright Hospital, for appendicitis. She had been troubled with cramps in the right side of the abdomen for three months before that. These cramps came on at irregular intervals, and lasted for a few days. The appendix was four cm. long; it was gangrenous in the proximal third, and there was a perforation. The appendix was removed and the stump was touched with carbolic acid followed by alcohol. A cavity of pus was found in the left side of pelvis and in the left hypochondrium. The wound was partly sutured and partly drained. The patient left the hospital in good condition; the discharge diagnosis was acute gangrenous appendicitis with advancing peritonitis.

After the operation the patient was well for five months. Then she noticed a small lump in the lower part of the abdomen on the right side: for two months there had been a red area on the left side of the abdomen. In June, 1905, she was operated upon at the Sydenham Hospital for a supposed abdominal tumor. The supposed tumor could be removed only in part. She was in the hospital for three weeks. One week later, in July, 1905, she was again operated upon at Gouverneur Hospital because the wound had not healed. Some further tumor masses were removed, a piece of which was examined by Dr. Norris, who reported it to consist of chronic inflammatory tissue. She was discharged from that hospital in October, with a diagnosis of sarcoma.

For four months after that her wound was dressed at St. Luke's Hospital. She was then a patient at St. Luke's Hospital until last August. Since her discharge from that hospital she had had pain in the left side of the abdomen and there had been a red area present. She had grown very



much thinner; had never vomited blood, but had passed blood by the bowels; there had been no jaundice. She complained of loss of flesh and strength, and of the mass in the abdomen.

On admission to our hospital the examination showed the following:

General condition: Very much emaciated; marked pallor; subicteric hue to skin; liver extended three fingers below the free border, not tender; large scar in median line involving umbilicus, scar two inches in greatest diameter. There was an irreducible hernia at the position of the scar of the appendicitis operation. On the right side of the abdomen there were several sinuses which hardly admitted a probe, the openings of which were not surrounded by any granulations. The rectal and vaginal examinations revealed a bulging.

While she was in the hospital she ran an irregular temperature, which usually reached 103° or 104° F. The leucocyte count was 10,000, of which the polynuclears constituted 94 per cent. The stool was examined for blood, but none was found. The urine was of a specific gravity of 1.012 to 1.020. There was a faint trace of albumin, and microscopically there were seen a few epithelial and hyalogramgranular casts.

On December 23 there was a hemorrhage from one of the large abdominal veins in the region of the umbilicus. The patient became progressively weaker and died on December 27.

As regards the clinical diagnosis, it was at first thought that there might be an intra-abdominal streptothrix infection, but examination of the pus expressed from the sinuses showed only streptococcus. It was then believed that there was an inflammatory process in the abdomen of unknown causation.

The post-mortem examination showed the following: In the lower part of the abdomen there was a large sacculatation of clear fluid. The intestinal coils were markedly adherent to each other. In the mesentery there were numerous pus tracts. The lymph nodes were of the same character as those to be later described. At a number of places in the abdomen there were masses of fibrous tissue due apparently to the healing of purulent foci. There was a particularly large mass at the root of the mesentery. At the site of the appendix operation there was a mass of inflammatory tissue. The sinuses were found to lead directly into suppurating veins in the mesentery. The portal vein was found to contain pus and old thrombotic material; the wall was necrotic; and the branches in the liver were involved. The splenic vein was not involved, but was dilated. The inferior mesenteric vein was found to contain old and recent thrombotic material. The liver was enlarged, congested and cloudy. Many branches of the portal vein in the liver contained pus, and about them there were numerous small and large abscesses, some old and partly healed, some consisting of yellow firm infiltrations.

All of the abdominal lymph nodes, even those along the iliac vessels, were found to be diseased. Most markedly changed were those near the hilus of the liver, the nodes in the mesentery and the nodes along the aorta. The nodes were large, some contained pus, some contained yellow cheesy areas and in a number of these areas there was a deposit of lime. In some of the nodes the cheesy areas were surrounded by fibrous tissue. The spleen was moderately enlarged and pale. The kidneys showed parenchymatous degeneration. The lungs contained a few recent and old abscesses. Some of the abscesses gave evidence of advanced cicatrization. The bronchial nodes showed the same changes

as the abdominal lymph nodes. The heart showed no changes of importance.

The microscopical examination of the various tissues revealed, in brief, the following:

The bronchial lymph-nodes showed areas of complete necrosis, with a deposit of cholesterin crystals. The liver showed purulent pylephlebitis and abscesses in various degrees of organization. Mesenteric lymph nodes showed purulent inflammation with secondary fibrosis and also areas of necrosis.

In the course of the bacteriologic examinations streptococci were obtained from the following: Abscesses of the lung, liver, portal vein, and some of the bronchial and mesenteric nodes. As it might have been suggested that the lesions in the nodes looked like tuberculosis, the material from a number of the nodes was examined for tubercle bacilli, but none was found. A number of guinea-pigs were inoculated subcutaneously and intraperitoneally with emulsions made from the bronchial and mesenteric nodes. None of these guinea-pigs developed tuberculosis.

We have here, then, a case of intra-abdominal inflammatory disease following appendicitis, which lasted, according to the history, for two years. The first impression we had of the case was that there was in the beginning a pylephlebitis due to infection from the appendicitis, and that then the lymph nodes in the abdomen and chest were involved. But careful consideration of the clinical history and of the lesions led us to believe that there is a probability that the infection may have been carried first to the lymphatics and lymph nodes, and then secondarily to the veins. The lesions of the lymph nodes looked much older than the other lesions.

The case appears to have had a longer duration than any case on record. Very few cases have been described in

which a suppurative pylephlebitis has lasted longer than two or three months. In a series of twenty-eight cases tabulated by Dr. Langdon Brown, it was found that in four the duration was under two weeks; in one, two weeks; in five, four weeks; in three, five weeks; in eight, seven weeks; in two, eight weeks; in two, ten weeks; in two, twelve weeks; in one, four months; and in one, eight months.

The lesions in our case point to a possibility of healing in cases of suppurative pylephlebitis. Some years ago one of us (Libman) presented to the Society a case in which the lesions in the liver and portal vein had practically healed. The patient died from an abscess in the mesentery with peritonitis due to rupture.

Rolleston, in his book on diseases of the liver, discusses the question of whether suppurative pylephlebitis can end in recovery. He doubts any reported recoveries in cases in which the liver was not seen. He refers to a case described by West,<sup>1</sup> of multiple abscesses of the liver secondary to appendicitis, in which there was supposed to have been a recovery; but in this case there was no definite proof of the existence of a pylephlebitis.

A case of interest was described by Goodhart.<sup>2</sup> At the autopsy of a boy of eighteen, which was performed after an illness lasting ten months, there was found an occlusion of the portal vein, with scars with caseous centers in the liver. He thought that suppurative lesions due to appendicitis had resulted in cicatrization. The cause of death was a perforation of an ulceration of the descending colon, which ulceration he believed was possibly due to portal obstruction and amyloid disease.

A supposed case of recovery was reported by Treves, but a perusal of the clinical history leads us to doubt the

(1) Trans. of the Clinical Society, XVII, p. 126.

(2) Trans. of the London Path. Society, XXXII, p. 137.

validity of the case, an opinion shared by Dr. Rolleston in a personal communication.

Langdon Brown<sup>3</sup> in his paper states that suppuration in the mesentery and in the lymph nodes is probably not infrequently the cause of infection of the portal vein. He believes this to be the usual course of the disease, an opinion with which we can not coincide, for we have seen in the operating room cases of appendicitis of one or two days' duration in which the branches of the mesenteric veins were already involved. Brown bases his opinion on two cases. In the first there had been an inflammation of the appendix, with occlusion of the mouth of the appendix and suppuration of the mesenteric lymph nodes and pylephlebitis. He believed that the appendicitis first healed and that the lymph nodes were infected and then infected the veins. In a second case of his there was no focus in the abdomen except calcareous and caseous nodes at the hilus of the liver. He cites a case similar to the last, which was described by Sturges, and four cases described by Fredrichs. We believe that the most significant observation, as regards the primary infection of the lymph channels in some cases of pylephlebitis, is a case described by Cruvelhier, in which there were liver abscesses with infection in the sheath of the portal vein without lesions in the interior of the vein.

### *Discussion.*

DR. CHARLES NORRIS asked Dr. Libman whether the lymph nodes were examined for spirochetes.

DR. LIBMAN said that spirochetes had not been particularly looked for. There was such a straightforward history of inflammatory disease that it was not believed that specific disease came into the question, and the microscopic examination showed that no evidence of specific disease was present.



DR. J. H. LARKIN thought that Dr. Libman's explanation of the case was very unsatisfactory. He thought that perhaps because of the long duration of the case Dr. Libman had allowed the lymphatic theory to overshadow the theory of ascending infection. Unless Dr. Libman was able to give a clear idea of why he thought this infection was through the lymphatics, Dr. Larkin thought it best to hold to the theory of ascending infection through the venous circulation. He did not see how the lesion in the liver could be explained on the basis of lymphatic involvement in a case which had had such a long duration.

DR. LIBMAN said that he had for a time also been of the opinion that the case was one of primary portal infection, but on considering the specimen carefully he had come to the conclusion that it would be an error to entertain this view only. The clinical history at the onset of suppurative pylephlebitis is generally very severe. The patients have repeated chills and fever, and such a patient would not have been sent out of a large New York hospital as cured. There is no record that she left the hospital with fever. But it is possible that a person could have a slowly developing lymphadenitis without marked symptoms. As a matter of fact the first symptom which the patient noticed herself, after a time had elapsed, was a lump in the right side of the abdomen. A careful examination showed that the thrombi in the inferior mesenteric vein were more recent than those in the trunk of the portal vein, and what is most significant is the fact that the lesions of the lymph nodes, especially in the mesentery and about the portal fissure, were much further advanced than the lesions in the portal vein or liver. Dr. Libman thought that one must consider in this case a primary lymphatic involvement as well as a primary involvement of the vein.

DR. NORRIS asked about the condition of the pancreas in this case.

DR. LIBMAN answered that it was normal.

A CASE OF TYPHOID FEVER IN AN INFANT. A  
CASE OF GENERALIZED INFECTION IN AN  
INFANT WITH A BACILLUS OF THE PARA-  
TYPHOID GROUP. A CASE OF UNIVERSAL  
FETAL HYDROPS.

A. M. PAPPENHEIMER, M.D.

The first case was that of a child, six months of age, who was admitted to the service of Dr. Lockwood on April 5, 1906. In the hospital history the only noteworthy points were the absence of any previous illness, and a recent exposure to measles. Later it was ascertained that the mother was also ill of typhoid fever at the same time. The child had been breast fed at first, but for the last few months had been fed on condensed milk and barley water. Six days before admission it suddenly became feverish, and refused food, and in this condition, which persisted, was brought to the hospital. There had been no conjunctivitis, cough, epistaxis, or rigidity of the neck noticed. On admission the temperature was  $104^{\circ}$ , pulse 160. The child was well nourished and developed; but was restless, apparently delirious, and looked very ill.

Physical examination showed an extensive maculo-papular rash on the trunk and upper extremities, a coated tongue, and a palpable spleen. There were no meningeal symptoms, and no abdominal distention. Until its death, which occurred on April 15, or ten days after admission, the temperature persisted high, ranging between  $102^{\circ}$  and  $105^{\circ}$ . During this time, the spleen was regularly palpable. There was, at times, slight abdominal distention. The stools, which at first were yellowish, toward the end became greenish with mucus and slight traces of blood. A general bronchitis developed. The possibility of measles being excluded

from the character of the rash, the subsequent course of the illness led to a tentative diagnosis of typhoid fever. Two attempts to isolate the typhoid bacilli from the stools were unsuccessful. A positive Widal reaction was returned from the Board of Health on April 7, although the dilution was not stated. With a laboratory culture, a positive reaction could not be obtained higher than 1-10. Dr. Hastings also reported a negative agglutination reaction.

Leucocyte counts on April 8 and 14 were 6,700 and 8,200 respectively, the lymphocytes forming about 60 per cent. of the total.

The necropsy, which was performed twenty-four hours after death, was limited to the abdominal and thoracic viscera. Briefly, the only noteworthy lesions found were the following:

The posterior portion of the lungs was slightly atelectatic, and there were a few small wedge-shaped hemorrhagic infarctions.

The liver was fatty, and on the surface there were a few hemorrhagic punctae. The gall-bladder was normal. Sections showed a few typical small areas of focal necrosis.

The spleen at autopsy was not noticeably enlarged. The kidneys showed acute parenchymatous degeneration, and, microscopically, small areas of acute interstitial nephritis. The stomach contained a small amount of mucus, but otherwise appeared normal.

The small intestine was entirely free from ulceration. Peyer's plaques were visible, and a few near the cecal region seemed very slightly swollen, and were pink in color. The solitary follicles were not microscopically distinguishable. The small intestine contained thin, finely divided feces. Microscopically, the plaques and follicles were hyperplastic, with small areas of necrosis in the centers of the follicles.

In the large intestine the mucous membrane appeared

slightly thickened, rough and mammillated but was free from ulceration. The solitary follicles were not visible. There was a moderate enlargement of the mesenteric lymph nodes, the largest in the ileocecal region measuring about 3 cm. in its longest diameter. On section they were dark pink in color, and very succulent, and microscopically showed the usual hyperplasia with necrosis in the germinal centers and marked hyperemia.

Pour plates were made from the spleen, using Hiss plate medium and agar. All the plates showed numerous colonies of a slightly motile Gram negative bacillus. The transplants yielded pure culture of the typhoid bacillus, as identified by its fermentation reactions, and other cultural characters. In a fresh broth culture, the motility was active. The agglutination reactions with an immune rabbit serum of maximum titer of 1-30,000 was positive after three hours at 1-10,000, and after twenty-four hours at 1-20,000.

The case, therefore, was definitely one of typhoid fever. The only noteworthy feature, from a pathological point of view, was the absence of intestinal ulcerations. Whether this is a constant feature of the disease as it occurs in early infancy, I am not prepared to say, since the number of authentic cases in children under a year are too few to permit of generalization.

\* \* \*

A second case, one of generalized infection with a bacillus of the paratyphoid group, is perhaps of greater interest. A Hungarian baby, three months old, was brought to the hospital on September 6. The history threw little light on the source of the infection. The baby had been fed with grocery milk, said to have been boiled and then diluted slightly with cold "standing" water. It had been poorly nourished since birth, vomited frequently, and cried often. Otherwise,

it had been fairly well until a week before admission, when it vomited and cried continually. There have been no cases of "fever" or other illness amongst the grown persons or children who came into contact with the baby. The child was emaciated, feverish, fretful, and appeared exceedingly ill. The veins of the head were dilated. The fontanelles were open and not depressed. The pharynx, ears, and nose were negative.

The lungs were filled with coarse rales, and there was a suspicion of bronchial breathing in the right axilla. The heart was normal. The abdomen was not distended or retracted. The liver and spleen could not be felt. There was no skin eruption, only a few excoriations. There was a suspicion of Kernig's sign, but no rigidity of the neck.

Blood examination showed 25,000 leucocytes, of which 47 per cent. were polynuclears, the rest lymphocytes. There were no plasmodia.

The temperature, which on admission was  $103^{\circ}$ , fell within twenty-four hours to normal; but from this time ran an exceedingly irregular course between  $104^{\circ}$  and subnormal. Two days later, there was noted in the history a stiffness of the neck and slight opisthotonos. The fontanelle was bulging.

The diagnosis in this case was made in a rather curious way. A specimen of the spinal fluid was withdrawn two days before death, and sent to the laboratory. The fluid was absolutely colorless and clear, and there was no sediment for microscopic examination. In order to assure ourselves of its sterility, a culture was made on blood serum. The following day there was an abundant, whitish growth, a smear from which showed a short, rather plump, Gram-negative bacillus. Although we considered this to be probably a contamination, we nevertheless planted it on various media, including dextrose, mannit, lactose, and saccharose serum-water, and Hiss



tube medium. The organism proved to be a bacillus of the paratyphoid group, since it produced gas in the Hiss tube medium, coagulated dextrose and mannit, and failed to ferment lactose or saccharose. Active motility was present in broth culture.

In the meantime, the child had died. The necropsy was not performed until forty-eight hours after death, but the body showed fair preservation. The conditions found were, briefly, the following: The gastro-intestinal tract showed no lesions of consequence. The Peyer's plaques were visible, but were not ulcerated, hyperplastic, or congested. The solitary follicles in the large and small gut could not be distinguished. The mesenteric lymph nodes were small, pale, and firm. The spleen was small, firm, dark red, and smooth on section; the follicles could not be seen with the naked eye. The kidneys were pale and moist, showing the usual appearance of an acute parenchymatous degeneration. In the lungs were a few areas of lobular pneumonia.

The only lesions of interest were found in the head. There was no meningitis, and the brain showed nothing abnormal save slight pial edema. The longitudinal sinus, however, from the vertex to beyond the torcular was filled completely with an adherent, friable, reddish grey thrombus, which extended a short distance on either side into the lateral sinuses. There was no thrombosis of the petrosal sinuses, however. Both middle ears contained purulent exudate.

We had, then, as the sole lesions, a suppurative thrombosis of the longitudinal sinus, a double suppurative otitis, and a lobular pneumonia, doubtless terminal. Bacteriologically, the case was one of generalized infection with a bacillus of the paratyphoid group. Pure cultures were obtained without difficulty from the spleen, from the bile, and from the thrombus itself. All the transplants examined showed an actively motile, small, Gram-negative bacillus, which fer-

mented dextrose and mannit with gas production, but which did *not* ferment lactose or saccharose, which produced an initial acidity in litmus milk, followed by a permanent alkalinity with partial clarification, and which rendered neutral-red-agar fluorescent within forty-eight hours. We have not as yet been able to procure any immune sera to determine the agglutinative relationship of our strain to the different types of paratyphoid.

Microscopic sections of the various organs have shown nothing of special interest, and a description of the histological findings may therefore be omitted. The case is presented as an instance of paratyphoid infection in a three months infant.

\*       \*       \*

Hydrops Fetus Universalis is defined by Ballantyne in his book on Fetal Pathology as a "rare condition characterized by general anasarca, by the presence of fluid effusions in the peritoneal, pleural and pericardial sacs, and usually by edema of the placenta; and resulting in the death of the fetus or infant before, during, or immediately after birth." Isolated cases have been described from the time of Hippocrates, but Ballantyne, in 1900, was able to collect in all only seventy-odd cases from the literature.

The specimen which we have to present was obtained through the kindness of Dr. Max Schott, who sent the fetus to the laboratory for diagnosis, and supplied us with a clinical history.

The mother was twenty-six years old, a primipara. Her parents were living and well, and there was no personal or hereditary history of syphilis. Her last menstruation was in February of this year. Pregnancy appeared to be normal, and she was free from unusual symptoms until the middle of the sixth month, when it was noticed that her abdomen

*suddenly* became very much larger, and she developed edema of the feet. She also complained of extreme thirst, and consumed large quantities of water. The urine was free from albumin or sugar. On the morning of September 14, that is, about the beginning of the seventh month of gestation, the bag of water suddenly broke. Labor pains did not set in until later in the afternoon. Dr. Schott was called in the evening and found the external os almost dilated, but was puzzled by the peculiar shape and doughy consistency of the presenting part. The second stage progressed slowly but normally until the head appeared at the vulva. "Then," to quote Dr. Schott, "I tried to aid its passage with my right forefinger by way of the rectum, but this slight effort on my part was sufficient to sever the head from the trunk; it tore off and fell out. In a similar manner, the arm separated from the shoulder when I hooked my finger into it in order to exert some traction on the body." Strong pains continued, and the rest of the body was expelled without difficulty. The placenta, when expressed, was found to be unusually large, irregular, friable, and edematous. The puerperium was rapid and uneventful; the only feature of note was the serous character and copiousness of the lochial discharge.

The fetus presented a really remarkable appearance. The preserved specimens fail to convey an adequate idea of it, and a photograph taken before the fetus was dissected unfortunately did not succeed. The general dropsy in this case was extreme. The features were swollen and distorted; the eyes were closed; there were deep grooves at the root of the nose and between the mouth and cheeks; and, indeed, the livid, puffy face curiously resembled, on a small scale, that of a morgue "floater."

The subcutaneous tissues everywhere were distended with serum. The dorsum of the hands and feet and the labia were perhaps the most edematous regions. Wherever the

skin was incised fluid exuded freely. The serous cavities, thoracic, pericardial, and peritoneal, were likewise filled with clear yellowish fluid of low specific gravity. The lungs were entirely unaerated and pressed against the vertebral column.

Aside from this general water-logged condition, no gross lesions or anomalies were discovered. The adrenals and kidneys appeared rather small for the size of the fetus, but save for a moderate pallor, were in no wise abnormal. The liver and spleen were very friable, but not otherwise remarkable. The intestines contained meconium; the mesentery was short. The thyroid, thymus, pancreas, bladder, and the other viscera appeared entirely normal.

The microscopic sections have not been of much assistance in revealing a cause for the condition. The kidneys show no clear evidence of nephritis, although there appears to be more than the normal number of leucocytes and round cells in the interstitial tissue. In the skin, the cutis consists of an edematous embryonic connective tissue, with numerous collagenous fibrils forming a loose meshwork. Capillaries are abundant, and there are plenty of developing sweat ducts. Fat cells are few and poorly developed. The papillae are rudimentary. The elastic fibers are present, but stain very faintly and show no regular disposition. The thyroid contains no colloid, and the cells are heaped up in the alveoli. The thymus is normal.

Although our study is very incomplete as yet, it is hardly likely that a more careful examination of the tissues will disclose a cause for this obscure and interesting condition. It may, therefore, be worth while to summarize very shortly the few clinical and pathological facts that are known. The etiology appears to rest entirely upon speculation. Maternal nephritis with dropsy has been present in a few of the cases, but this is so frequent an accompaniment of pregnancy, and fetal dropsy is so rare an outcome, that no serious

importance can be ascribed to their coincidence. Careful microscopical examinations of the fetal organs have been recorded in but nine cases (Ballantyne). The majority of these showed little indisputable evidence of nephritis, although in two of the cases there was complete cystic degeneration. The placental findings are inconstant, and may well be secondary. Some of the recorded cases have shown cardiac anomalies—stenosis of the pulmonary ostium, defective septa, or premature closure of the foramen ovale—and the attempt has been made to explain the general hydrops upon purely mechanical grounds. As many of the cases, however, have shown normal hearts, and, conversely, as these congenital cardiac defects frequently occur without edema, the causative relationship is not clear.

Microscopic examination in several of the cases has shown a stagnation of the leucocytes in the liver, spleen, and marrow, and the sections from the liver in our case show a similar condition. This has been interpreted by Sanger as a leukemic infiltration, and the disease regarded by him as a sort of fetal spleno-myelogenous leukemia. Even if this were a constant finding, it would scarcely explain the hydrops. The cause for the hydrops, therefore, is still undiscovered. The dropsical infants are born oftenest to women over thirty, and very rarely, as in our case, to primiparae. There appears to be a tendency for the condition to recur in later pregnancies. Polyhydramnios is the rule; a few of the labors are recorded as dry. The fetus, if born alive, dies within a few hours; often, because of the friability of the tissues, it is badly injured during delivery. The danger to the mother appears to be slight, aside from the increased mechanical obstacle to labor. A successful convalescence is the rule.



A CASE OF DIFFUSE BILATERAL HYPERTROPHY  
OF THE FEMALE BREASTS.

WILBUR WARD, M.D.

The following case of diffuse bilateral hypertrophy of the female breasts represents a rather uncommon clinical and pathological condition and is, therefore, thought to be of sufficient interest to present here.

The patient, who first came under observation on February 1, 1906, was an unmarried mulatto woman, twenty-one years of age. The family history was negative. She herself had never had any illness confining her to bed. Menstruation began at fourteen, and was always regular, the duration being five to six days, with moderate flow, accompanied by a moderate degree of general pelvic discomfort. Two years previous she had given birth to a healthy child after a normal pregnancy and labor. The child was nursed by the mother and the breasts appeared normal in every respect. At the age of five months, the child died from some unknown cause and the mother experienced no difficulty with the breasts, although she took no especial care of them. Shortly after that time, menstruation began again and was perfectly normal until January, 1906 (one month before admission), when she did not menstruate. Last menstruation, December 25, 1905.

*Present Illness.* In June, 1905, eight months before admission, she first noticed a small firm lump in the outer and upper quadrant of the right breast. This was not well defined and was slightly painful and tender to the touch; and the overlying skin was very slightly reddened. The patient thought it was a bruise and did nothing for it. The lump gradually grew, however, and extended to all parts of the breast, which became markedly swollen. This increase in the size of the breast continued, and was accompanied by

almost constant pain, dull and aching in character, while the whole breast was very tender.

In January, one month, before she came under observation, and seven months after the swelling began in the right breast, a small swelling appeared in the upper and outer quadrant of the left breast, exactly similar to the original swelling on the opposite side. This has grown in the same way, and for the past two weeks the breast has rapidly become larger, and is the seat of the same kind of dull, aching pain, practically continuous. On admission the general condition was fair and there were no symptoms of any disease.

*Physical Examination.* The patient is a mulatto woman of small frame, about five feet two inches in height, weighing about one hundred pounds. She is poorly nourished, with little subcutaneous fat; visible mucous membranes pale. Heart, lungs, abdomen, and extremities, negative. Vaginal examination showed that the uterus was slightly enlarged, in normal position, and not tender. Adnexa normal.

*Surgical Condition.* The breasts are seen to be considerably enlarged, the right more than the left. They preserve fairly well their normal shape, extend downwards over the upper part of the abdomen, and stand out rather prominently from the chest wall. Unfortunately no measurements were taken. The nipples are sound and erect; the areolae are normal. The skin shows a slight diffuse redness without any excoriation; it is apparently neither thickened nor thinned. The subcutaneous veins are enlarged. Upon palpation both tumors are found to be of the same consistency throughout, the peripheral portions appearing the same as the central. They are of a uniform firmness, with a very slightly irregular surface, giving one the impression that the whole mass is made up of many smaller fused nodules. This impression is elicited only by very light palpation, the sensation being lost on firmer pressure. The masses are very sensitive to pres-

sure, the tenderness being general and not more marked in one place than another. The overlying skin is freely movable except at the nipples, and the masses are readily moved upon the underlying muscles. No colostrum is present. No enlarged axillary nodes can be found.

*Clinical Course.* As the patient suffered increased pain of a dragging character when up and about, seemingly due to the weight of the breasts, she was put to bed, and the breasts were covered with ichthyol ointment and supported. At the same time she was given potassium iodide gr. x and the iodide of mercury gr.  $\frac{1}{4}$  t.i.d. Examination of blood and urine was negative (leucocytes 8,400, 83-17). The local condition remained approximately the same, the pain diminishing with varied external applications up to a certain point, and then persisting with acute exacerbations from time to time. The redness of the skin disappeared early, and did not return. The breasts, however, constantly increased in size.

The patient was kept under observation in the hospital for nine weeks. During that time menstruation did not appear, the uterus and with it the lower abdomen continually enlarged, and a diagnosis of probable pregnancy was justifiable.

The condition of the patient, however, was not satisfactory. The pain was continuous and extreme, the enlargement of the breasts progressive. Practically no nourishment was being taken and the patient slept but little because of pain in the tumors. On April 5, therefore, the breasts were amputated. Two operators, one working on each side, removed them simultaneously through double-V shaped incisions, including the nipples and a segment of skin between the arms of the incisions. No difficulty was found in easily stripping them off the pectoralis major, and enucleating the entire masses. The axillae were not opened.

Thirty-six hours after the operation the patient began to

complain of intermittent abdominal pain and in a few hours delivered herself of a fetus apparently in the fourth month of development. There were no sequelae. The wounds healed by primary union and in the course of two weeks the patient was discharged entirely relieved.

The tumors removed show that the pathological process has involved the entire breast tissue, no normal gland substance being left. The masses are of even consistency throughout from the periphery to the center. The tissue is firm, and on section grayish white, and the whole mass is divided by a few connective tissue bands into large lobuli. The tissue within the lobuli is homogeneous, firm, and very slightly granular. There are no cysts or necrotic, suppurating, or hemorrhagic areas. Blood vessels are small and few in number.

The microscopical picture is the same whether the sections are taken from the periphery or the center. The essential lesion is the production of an enormous number of gland tubules, embedded in an interlacing connective tissue framework; both the tubules and the fibrous tissue correspond closely to these elements as found in the normal resting gland. The glands are simple, or in some places have assumed very irregular forms with narrow lumina, in other places are moderately dilated. They are lined by one layer of cells, usually low cylindrical or cuboidal. The connective tissue is relatively scanty in amount and very cellular. It presents nothing abnormal except an infiltration with cells of the plasma type and in some places a marked degree of edema. Vessels are few in number and small. Fat is almost entirely absent except in the large septae.

Cases of this character have been described by many observers and have almost universally been divided into two groups; those occurring at the time of puberty and those occurring during pregnancy. Nearly all the cases reported can

be put into one of these two groups. Kirschheim, in 1901, collected from the literature thirty-nine cases of bilateral hypertrophy of the breasts; in twenty-seven the appearance of the disorder was at the time of puberty and in nine during pregnancy, leaving three cases in neither group.

The cases appearing at the time of puberty usually give a history similar to the history of this case. The breasts gradually take on growth, but instead of stopping when normal adult size has been reached the process continues and goes on indefinitely. The extent of the enlargement varies greatly. Some grow to enormous size, several cases being reported where the masses extended to the thighs. In the average case they do not extend much below the navel, for by the time they have enlarged to such an extent, relief by operative methods is usually sought.

The cases occurring during pregnancy are somewhat different. The increase in size usually begins during the second month and is rapid and progressive for from two to five months. Then there is a stationary period, and after delivery a rapid reduction in size usually occurs. The reduction in size practically never takes place in the cases occurring outside of pregnancy.

There are few symptoms. In most cases the progressive enlargement is the only symptom until the breasts have reached a moderate size; then there is dragging pain or ache, apparently due to the weight and pulling on the chest wall. In a few cases pain of a sharp, stinging, lancinating character is present early.

The enlargement of the breasts is always diffuse; their consistency is even throughout. There is never any circumscribed tumor in the breast, with parts of the latter of normal consistency. The axillary nodes are seldom enlarged unless there is some ulceration or excoriation of the skin overlying the tumor. Foges reports an interesting case where



there were accessory mammæ in each axilla, which shared in the hypertrophy.

There is usually no impairment of the general health until the breasts have enlarged considerably. That the resulting condition of anemia and malnutrition is due solely to the mere physical presence and inconvenience of the masses is shown by the fact that in all such cases removal of the breasts has caused a prompt return to normal health.

In all cases of true hypertrophy the tumor is made up microscopically of the two main constituents of normal breast tissue, glandular structures and connective tissue, in varying proportions. On the one hand, the fibrous tissue is relatively greatly in excess with but a few atrophied or compressed gland tubules. At the other extreme, as in this case, the glandular structures are enormously developed, with but relatively small amounts of fibrous tissue. All intervening gradations have been observed. As a general rule it has been found that in those cases developing during puberty, the fibrous elements preponderate, while in those cases occurring during pregnancy the glandular elements are in excess.

The prognosis for spontaneous diminution in size for those cases occurring at the time of puberty is almost nil. All kinds of local applications combined with internal medications have been tried without result in almost every case. In the majority of cases amputation has been resorted to; relief is immediate and absolute.

In those cases appearing in pregnancy the prognosis is quite different. In most cases there is a rapid return to normal after delivery, although the condition may return during a subsequent pregnancy. Amputation has been done in these cases, but the opinion of most observers is that operation should be deferred until the effects of delivery are noted.

Our case does not fall properly under the head of en-

largement during pregnancy as the history is clear that the onset antedated conception by at least six months. The condition was probably augmented by the pregnancy. At all events, the pain was so severe and incessant, and the patient so desirous that something be done on that account, that operative measures were instituted. Whether these might have been longer deferred is a question for debate.

### MID-WINTER EPIDEMIC OF DYSENTERY OF THE HISS-RUSSELL TYPE, INDIRECTLY TRACE- ABLE TO MILK.

HANS ZINSSER, M.D.

During February, 1907, the writer had occasion to examine the milk used in the children's ward of a New York institution. For some time diarrhea of a dysenteric type had prevailed among the children, which had resisted treatment. At the time of the milk examination five children were ill, three of them very severely, having very frequent stools, small in size, with much mucus and occasionally small flecks of blood. The patients were in a condition of rapidly progressive inanition. These cases had obviously developed in the hospital and were therefore a source of worry to the medical staff.

The milk was examined at the request of the attending physician, to whom the writer owes the privilege of reporting the cases, and was found to contain about 350,000 organisms to the cubic centimeter. While an attempt was made to identify these, nothing could be found which would account for the existing condition. Nevertheless, in view of the inconclusiveness of the qualitative bacteriological examination

of a milk so rich in organisms, the numerical result was deemed adequate reason for holding the milk responsible, and the feeding was completely changed. Three of the cases were at this time too ill to recover. The two which were in fair condition, however, promptly recovered. No new cases developed in the ward.

From the stools of one of the cases which recovered, the writer isolated an organism, the description of which is as follows:

The organism was a Gram-negative bacillus, morphologically much like *B. coli*. It was non-motile and non-sporebearing and seemed to grow as well aerobically as partially anaerobically. Upon agar and gelatin its growth resembled *B. coli communis*. It did not fluidify gelatin. No indol was produced. In fermentation tubes of dextrose, lactose and saccharose, no gas was formed. Upon Hiss tube medium it formed no gas and remained confined to the line of the stab. On the sugar-serum-waters it gave the following reactions:

Dextrose	+	Acid and coagulation.
Galactose	+	Acid and coagulation.
Levulose	+	Acid and coagulation.
Mannit	+	Acid and coagulation.
Maltose	—	Slight acidity.
Lactose	—	
Saccharose	—	
Dextrin	—	
Dulcit	—	
Litmus milk	—	

The organism described may thus be placed among the mannit-fermenting dysentery organisms, differing from the Flexner and Rosen types by its inability to ferment maltose, lactose, saccharose, or dextrin. It seems, as far as its fermentation powers are able to show, to be identical with the *B. "Y"* of Hiss and Russell. This type was found by Shorer

and Knox to be the most frequent among the types isolated by them from dysentery patients.

The cases are reported for two reasons. In the first place, it seems to the writer that in the case in question the connection between the milk and the infection with the organism is unusually clear. In the second place, the cases occurred in mid-winter in a Northern climate, the milk coming from not further than fifty miles and being handled during transit with reasonable precautions.

### *Discussion.*

DR. W. H. PARK asked whether he had understood rightly that the organism had produced no indol at all.

DR. ZINSSER said that it had not produced indol, and that in placing it in this group he had been guided by Hiss' first report which stated that his organism "Y" did not produce indol.

DR. PARK said that this bacillus was distinguished from others of the group with which Dr. Zinsser had classed it by the fact that it did not produce indol. All the others of this group, the Hiss "Y", the Mount Desert, etc., did produce indol. The Shiga bacillus, however, did not. He believed that in these slight epidemics there would often be found strains of bacilli having slight variations from the characteristic types.

---

## A CASE OF PERITONEAL INFECTION BY BACILLUS TYPHOSUS WITHOUT INTESTINAL PERFORATION.

HANS ZINSSER, M.D.

Dr. Hans Zinsser reported a case of typhoid fever occurring at St. Luke's Hospital, in which there was an unusual location of the bacillus. The case was that of a woman over fifty years of age, who entered the hospital on the thirteenth day of her illness, which was very obviously typhoid. She gave a typical history. Temperature was  $104^{\circ}$ ; pulse slow, 84; leucocyte count 7,000; polynuclear leucocytes 64.5 per cent. Widal reactions were rather unsatisfactory, but she nevertheless had all the clinical signs of typhoid, enlarged spleen and rose spots on the abdomen and back. She was treated as a typhoid patient and nothing of interest occurred until the fourth week of her illness, when she suddenly, at about four a.m., developed pain in her abdomen which was persistent. Perforation was suspected and she was carefully watched and leucocyte counts were made frequently. There was no change in the symptoms, and the leucocytes rose to 16,600. It was believed that operation was advisable, and this was done at about 8.45 p.m. When the abdomen was opened the peritoneum was found to contain a small amount of turbid fluid, some of which was taken out under sterile precautions. The intestine was congested. In the small intestine there was a slight constriction, and below this the intestine there was a slight constriction, and below this the intestine. The only other unusual thing noticed was that the omentum near the constriction was adherent to the gut, and there were fresh inflammatory adhesions. A very careful search for perforation was made and none could be found. The pelvis was normal. In the fluid, which was sent to the laboratory for examination, there was found a pure



culture of *B. typhosus*. The patient at the time of the report was on the way to convalescence. The explanation of the finding of the bacillus in the exudate without a perforation can rest only upon conjecture. The most reasonable explanation seems to be that at the seat of the constriction there may have been a deep ulceration, the typhoid bacillus working its way through this.

### *Discussion.*

DR. E. LIBMAN asked whether there had been sufficient fluid to make a microscopical examination in order to determine whether the turbidity was due to red blood cells or to leucocytes; and also whether there had been sufficient bacilli to be seen before the culture was made.

DR. ZINSSER said that no morphological examination had been made.

---

## NOTE ON INVOLUTION FORMS OF SPIROCHÆTE PALLIDA IN GUMMATA.

JAMES EWING, M.D.

In the earliest observations on syphilitic tissues stained by Levaditi's method, it was apparent that while spirochæte pallida is an extracellular parasite, yet it suffers extensively from phagocytosis and undergoes progressive intracellular digestion by several type of cells, not only in primary lesions but also in secondary and in congenital syphilis. So prominent and constant is this process that one may safely conclude that phagocytosis is an important, if not the chief, means of defense of the organism against syphilitic infection. The

morphology of the intracellular digestion of *S. pallida* has been fully described and illustrated by Ehrmann<sup>1</sup> and by Gierke.<sup>2</sup>

In a series of chancres, cutaneous lesions, and congenital syphilitic tissues, I have been able to identify, without difficulty, the appearances described by these authors; and I believe that their interpretation of the fragmented and deformed structures is correct. Several rather distinct stages of the destruction of the spirochætæ may be recognized in cases which, on account of the presence of intact organisms must be regarded as undoubted syphilis.

I. The englobed spirochæte may present its usual form, except that it is broken up into two or more fragments, each of which appears as a short pallida.

II. The organism may appear as a chain of granules which outline a complete spirochæte.

III. A characteristic appearance is the radial arrangement of several short fragments of spirochætæ at one or both poles of the nucleus.

IV. Frequently one encounters an organism which incloses a circular mass of protoplasm within the whole or a part of the spirally wound body.

V. The later stages of digestion often leave the cell thickly studded or even distended with jet black granules. Although no definite organism can be identified<sup>3</sup> in such cells, nevertheless their appearance is characteristic, and I have not been able to find such cells in a considerable series of tumors and necrotic lesions other than syphilis.

VI. Finally, the cell may contain several foci of compact granules of the above type, and eventually the granules may lose their capacity to take up the silver and appear as yellow-

(1) Cent. f. Bact., XLIV, 1907, p. 223.

(2) Ibid., p. 348.

ish granules, in which condition they are no longer recognizable as derivatives of spirochætæ.

I have not been able to find the compact homogeneous black masses depicted by Gierke in polynuclear leucocytes.

Not only do the common phagocytes, polynuclear and mononuclear leucocytes, englobe the spirals, but fibroblasts and parenchyma cells, as those of the liver, pancreas, adrenal, and testicle, may take them up in large numbers, so that the appearance of many syphilitic tissues after Levaditi's stain tends to arouse suspicion that the supposed parasites are altogether too numerous to be genuine. However, the very large numbers of spirals occurring in many lesions and the abundant transitional forms between intact spirochætæ and their granular detritus leaves little doubt, I think, that the presence of *S. pallida* may be recognized with certainty from many of the late stages of intracellular digestion.

The importance of these observations lies in the fact that the whole field of the pathological histology of syphilis must be traversed by means of Levaditi's method, if the nature of many conditions is to be certified, as it now should be, by the discovery in each of them of *S. pallida*, and if this is to be accomplished, then the diagnosis must sometimes rest on the finding of the less characteristic forms which have suffered intracellular digestion.

In tertiary lesions this work will be especially difficult, for while numerous spirochætæ have been found in a few recent gummata, these lesions have usually been found free from readily recognizable parasites. In spreads of tertiary lesions stained by Giemsa's method, several observers have found isolated spirals, but only after prolonged search; while reports of the study of such lesions stained by Levaditi's method are scanty and usually negative. Reuter found a few *S. pallida* in syphilitic aortitis.

In a routine search through tertiary syphilitic lesions

during the past year, I have failed to find typical *S. pallida*; and owing to the danger of confusing structures of unknown origin with fragments of spirochætæ, I had come to regard the search for these organisms in gummata and old productive processes as of little value. Recently, however, a gumma of the testicle was encountered, in which, in addition to a very few slightly deformed spirochætæ, still recognizable as such, there were a great many cells containing large numbers of the fragmented forms enumerated above. A comparison of these cells with others found in chancres and in congenital syphilitic lesions leaves no reasonable doubt that this gumma contains a very large number of *S. pallida* in various stages of intracellular digestion.

The history of the case, for which I am indebted to Dr. John Rogers, is as follows: The patient was a well-developed subject of thirty years of age. He presented a painless tumor of the body of the testicle which had been steadily increasing for six weeks. There was no history of chancre or eruption; and no enlargement of the lymph nodes or other signs of syphilis could be found. The patient insisted on the removal of the organ. The testicle was moderately enlarged and a gumma, 1.5 x 1 cm., was found in the body and involving the tunica. Both layers of the tunica were thickened and infiltrated with blood.

The examination of sections of tissue stained by Levaditi's method resulted in the discovery of a very few spirochætæ showing the usual characters of pallida, except that they were short, not more than six or eight coils being present. Throughout the necrotic material, and more abundantly on the edges of the lesion, there were many cells containing small fragments of spirochætæ of the types described under classes III to IV. An interesting feature was the presence of many large phagocytic cells in and beyond the borders of the gumma, containing many black granules similar to those

resulting in the last stages of intracellular digestion of *S. pallida*. On the other hand, some of the best-preserved organisms were found well within the necrotic zone. These relations suggest that the destruction of the organisms had not proceeded far when the tissues became necrotic, and was to some extent inhibited by that event, while the better nourished cells beyond the necrotic zone were able to carry the digestion further and limit the spread of infection. It follows from the comparison of this gumma with others in which no spirochætæ or their derivatives could be recognized, that there is a progressive destruction of the organisms in these lesions, reaching in old cases a complete removal of all traces of spirochætæ. Hence there must be intermediate stages of the process in which the diagnosis of syphilis, if based on Levaditi's method, must rest on the discovery of extensively subdivided fragments and granules derived from digested spirochætæ, with entire absence of typical organisms.

The wisdom of attempting the microscopical diagnosis of syphilis in the absence of typical spirochætæ may very well be doubted, since, as pointed out by Saling, the structures which simulate spirochætæ after Levaditi's method are rather numerous.

But Saling's criticism has only served to define more exactly the positive histological characters of genuine spirochætæ; and the wisdom of attempting to recognize fragments of these parasites depends entirely upon the certainty with which they can be separated from tissue detritus. My present impression is that the partially digested parasites are, in many stages, quite characteristic, and amply so for identification. Among elements which may simulate spirochætæ may be mentioned borders of many varieties of cells, pigment granules in cutaneous chromatophores, fatty crystals or partly saponified fats, calcific granules, detritus from red blood cells, bacteria, and fibrils of the reticular tissue of



lymph nodes. None of these elements exactly reproduce intact spirochætæ; and I have been unable to find that any of them exactly simulate some of the appearances produced by the intracellular digestion of spirochætæ. If this conclusion proves reliable, then one who is fully familiar with the intracellular digested forms of *S. pallida* will be able to identify many syphilitic lesions by Levaditi's stain, which have heretofore been recognized by their association with other syphilitic lesions, or by the less certain general histological structure of luetic inflammation.

### *Discussion.*

DR. CHARLES NORRIS said that he had himself been rather disappointed in the few specimens which they had put through with the Levaditi method. In them they had been unable to obtain any evidences of spirochætæ, so that as a routine method of diagnosis to distinguish between tuberculosis and the various tertiary lesions of syphilis it was of little use.

---

## A CASE OF HYPERNEPHROMA OF THE ADRENAL GLAND: A CASE OF ANGIOSARCOMA OF THE FOOT: A CASE OF PERNICIOUS MALARIA WITH AUTOPSY.

G. R. SATTERLEE, M.D.

Dr. G. R. Satterlee presented a case of hypernephroma of the adrenal gland. The patient was a janitor, fifty-one years of age, who was admitted to the wards of Gouverneur Hospital, on August 12, 1907. He had been a moderate drinker up to twenty-eight years ago, but since that time

had not used alcohol. He had had gonorrhea. He had also had an attack of lumbago six years ago. Otherwise he had been healthy until four years ago, when he had had a sudden severe pain in the right side radiating to the right side of the sacrum and penis and down the thigh. Several times since then, perhaps ten or twelve, the patient had had similar attacks. He passed bright red blood after each attack of colic. For three and a half months back the patient had noticed that his urine was turbid, containing a slimy substance like pus. His general condition was that of a poorly nourished man. In the abdomen below the right costal border there was considerable tenderness and a definite tumor could be palpated to the liver. The spleen was not palpable. Examination of the urine on August 13, showed tenacious, cloudy mucus; specific gravity 1.015; neutral; much albumin; no sugar; many red cells and occasional leucocytes. Two days later, there was pale, cloudy mucus, many red cells and leucocytes; occasional granular casts. Tests for tubercle bacilli were negative. On August 17, urine showed dark brown cloud, red sediment; specific gravity 1.015; amphoteric; heavy trace of albumin; many red cells and leucocytes, fibrin and debris.

The patient was operated upon by Dr. John F. Erdmann, and the tumor and right kidney were removed. The tumor was an oval mass, 16 cm. long, 6 cm. thick, and 12 cm. transversely, and was intimately connected with the kidney, which was posterior to it. The lower part of the kidney was involved in the growth; the upper part was free. The ureter was free and a probe could be passed through the entire length. The cut surface of the tumor showed small yellowish nodules which were at first thought to be cheesy in character. The tumor was firm and had considerable resiliency. The surface was studded with small yellow nodules apparently about to break down. The cut surface of the kidney showed the

markings fairly regular; the capsule was slightly adherent; and the veins were congested. The cortex was 4 cm. in thickness, and pale; and the blood vessels were much congested. Microscopical examination of the tumor showed irregular lobules separated by fibrous tissue in which some infiltration with leucocytes had taken place. Some nodules were filled with typical adrenal cells in columns. The cells were surrounded by capillary blood vessels and had very fatty cytoplasm. There were a few large oval cells among them with two or three large oval nuclei placed near the center. In some, fatty particles and broken down debris filled up the lumen. There was a considerable amount of brownish pigment in the cells. Many of the lobules contained well defined glandular acini. The tumor was diagnosed as a mixture of adenoma and adrenal tissue, the larger part constituting what is known as hypernephroma. The examination of the kidney showed a combination of chronic parenchymatous with chronic interstitial nephritis. There were a few areas of necrosis suggestive of either tuberculosis or syphilis, but not characteristic of either.

The patient in this case made a complete recovery from the operation and so far had shown no signs of recurrence.

Dr. Satterlee also presented a case of angiosarcoma of the foot. The patient was a young woman, aged twenty-two years, who was first admitted to Gouverneur Hospital in April, 1905. Unfortunately the history notes of that time have been lost. She was admitted for the second time on January 7, 1907. The records note that the previous history up to March, 1905, was negative. At that time the patient noticed a tumor on the right ankle. She entered the hospital where the tumor was removed. After leaving the hospital she felt perfectly well and could walk. In October, 1906, she again had pain in her right ankle and on walking. She had lost weight for some time. On her ankle there was a scar

of a former operation and on the upper edge of the scar there were two nodular growths about the size of a chesnut. About half way up the right leg there was a firm growth. There was general enlargement of all the lymph glands, especially of the right inguinal, which were very hard and attached to the surrounding tissues. The tumors on the foot and leg were excised; none was attached to the bone. The pathological diagnosis was sarcoma, variety not stated.

The patient was again admitted to the hospital in October, 1907, when she walked with a limp in her right leg. Examination showed below the right internal malleolus the scar of a former operation; above this was a growth about the size of a hickory nut. On the inner side of the sole of the foot there was a small metastatic nodule. The patient said that since the operation in January, 1907, she had been perfectly well until four months ago when the growth on the ankle reappeared in the place of the former operation. At the third operation (October 2d, 1907) the growths were removed and skin grafts applied, by Dr. H. M. Silver. The growths had not invaded the deeper tissues to any extent.

One month after the operation recurrence of the growth rapidly took place, and amputation would have been advised except for the fact that the woman was six months pregnant.

Microscopical examination of one portion of the tumor supposed to be a lymph gland showed it to be of an irregular reticular structure, with very large and small spaces. Most of the spaces were lined with endothelial cells and filled with blood. Surrounding these spaces were fusiform cells with oval nuclei. In numerous places the blood had infiltrated the sarcomatous tissue to an extensive degree. No evidences of lymphoid tissue could be seen in this specimen. The specimen from the sole of the foot was about 0.5 cm. in thickness and occupied the subcutis. Microscopical examination showed large spindle-shaped sarcomatous cells closely

packed together. The specimen showed capillary spaces similar to the spaces in the first tumor. Around the walls of these vessels were cells closely applied to the endothelium lining the spaces. The ground substance was fibrous in character. In the superficial subcutis some of the lymph spaces contained masses of sarcomatous cells with a moderate amount of dark pigment. The diagnosis was angiosarcoma.

This variety of tumor has been classed by Sutton with endothelioma and perithelioma. Senn gives a description of angiosarcoma and says the consistency varies from that of a more or less jelly-like mass to considerable density. Angiosarcomata present usually a reticulated structure with the cells arranged in strands. The cells are epithelioid in shape. The ground substance is composed of all possible forms of connective tissue. Vessels are numerous and large and always capillary. In many forms the cells are closely grouped around vessels as if they had been developed in their walls. Blood cysts and hemorrhages are frequent. The masses of cells thus formed may be packed closely together or may be arranged in rounded groups. Angiosarcomata, Senn says, are quite rare and are most frequently found about the head. Other authors distinguish angiosarcoma, endotheliosarcoma and peritheliosarcoma. Dr. Satterlee would prefer to class his case as an angiosarcoma rather than a peritheliosarcoma.

Dr. Satterlee also described a case of pernicious malaria with autopsy. The patient was admitted to the Gouverneur Hospital on October 15, 1907, in the service of Dr. Francis Huber. The patient was a hard drinker, had had gonorrhea several years, but denied syphilis. He was twenty-six years of age, a sailor, and had been in New York only nine days after his last trip. He had spent the winter before in the south. About one week before admission he had suffered from loss of appetite, headache, fever, and chilly sensations



with general malaise. He had not noticed any blood in the stools or urine. On admission, his temperature was  $105^{\circ}$ ; pulse 120; respirations 42. The general condition was that of alcoholic delirium. The next day the temperature was  $99^{\circ}$ ; and the patient was slightly better. Examination showed a well developed, well nourished adult male. Sclerae and skin were somewhat jaundiced. The liver was not palpable; the spleen just palpable. The blood count showed 24,000 leucocytes, of which polynuclears were 56 per cent. The urine had a specific gravity of 1.018, and contained no albumin and no blood. On the morning of the second day in the hospital the temperature at five p. m. rose to  $103^{\circ}$  and at nine p. m. to  $105^{\circ}$ . The patient sank into coma and died at midnight after a chill lasting twenty minutes.

The autopsy was performed fifteen hours after death. There was slight jaundice, but no pigmentation. The heart muscle was pale and flabby. The aorta showed a slight fatty infiltration of the intima. The thyroid gland was enlarged to about three times its normal size. The spleen weighed one pound; the surface showed old interstitial splenitis. The liver weighed  $6\frac{3}{4}$  pounds; the surface was pale and mottled. The kidneys showed an acute parenchymatous nephritis. The brain was almost normal, and there was only a moderate amount of congestion in the blood vessels.

Smears of blood obtained at sixteen, twenty-four, and forty hours after the chill and at the time of death, were examined.

The first specimen showed an excessive number of ring forms fairly regular in shape, with moderate amount of fine pigment. In some fields over 75 per cent. of the red cells contained these deposits; most of them with one, but a large number with two, three, four, or even five parasites. The cells in this blood were small and many were crenated. Macrophages were fairly abundant but not as abundant as in

later specimens. The second specimen showed fewer ring forms. The specimen taken forty hours after the chill, or eight hours before death, showed few organisms. The red cells were much larger than at first and some ovoids were seen, with but very few ring forms in this specimen. Here there were some beginning segmenting bodies in the red cells in the peripheral circulation, containing apparently ten segments. The specimen of blood taken at the time of death showed an excessive number of ring forms, crescents and ovoids. Smears from the spleen showed every stage of growth of the organisms including ovoids and crescents and segmenting bodies containing from fifteen to twenty merozoites. All the former were characteristic of the tertian variety of the estivo-autumnal parasite.

---

## A CASE OF ARTERIOSCLEROSIS OF THE PULMONARY VESSELS.

HARLOW BROOKS, M.D.

Dr. Harlow Brooks described a case of arteriosclerosis of the pulmonary vessels occurring in a woman, thirty-four years of age, of foreign birth, who was suffering from the results of hemiplegia following cerebral hemorrhage. Her personal history was one of no importance except that she had had one miscarriage at the eight month; there was no other history pointing to syphilis. On general examination she showed a well defined double aortic lesion. She also suffered from chronic diffuse nephritis and the hemiplegia. This hemiplegia was rather remarkable in one respect, that is, the spastic condition ordinarily found was not present. The course of the disease was unimportant. At autopsy,

the heart showed double aortic and double mitral lesions, both very marked. The aorta and the large trunks were notably of smaller caliber than would be expected. The left ventricle was considerably hypertrophied. Both auricles were dilated and a thrombus was present in the right auricle. The right ventricle was considerably hypertrophied; the wall being about twice the ordinary thickness. The semilunar valves were perfectly functional as far as could be decided, though somewhat thickened. Just above the pulmonary ring there was a dilatation of the vessel, not large enough to be called an aneurism. In all the branches of the pulmonary artery were found large plaques of sclerotic change with raised yellowish masses jutting up into the lumen. Comparing this vessel with the aorta, the aorta was seen to be slightly diseased; while the wall of the pulmonary was not only extensively diseased but was as thick or thicker than the aorta. In addition, there was a pulmonary fibrosis which was very marked about the pulmonary vessels and not about the other trunks, as one would expect with the mitral and aortic lesions. Microscopically it was demonstrated that the thickening of the pulmonary artery extended through all the branches of the artery, even to the smaller. The case was interesting because all the cases of pulmonary arteriosclerosis which have been reported are those in which there was a primary endocarditis. In this case there presumably was not this cause.

The case then differed from the ordinary case as it has been reported in that it seems to have been primary in the vessels. Throughout the body there was a moderate degree of arteriosclerosis, notably in the brain, which was probably the cause of the hemorrhage which had taken place about three years before.

In looking over the literature, Dr. Brooks was surprised

to find the number of cases of arteriosclerosis in the pulmonary vessels. In analyzing his own cases he was also surprised to find that the pulmonary vessels stood seventh in point of involvement, while the visceral trunks were first. In all of these cases he had found evidences of a primary endocarditis.

As regarded the etiology of this case, although there was nothing definite, he was inclined to call it syphilis. All the corroborative evidence was a miscarriage at the eighth month, which was, of course, rather late for one due to lues. He thought, however, that it was safe to assume that the etiology was syphilis, largely on account of the gross and microscopic character of the lesions. His explanation of this particular case would be simply that it was like other cases of syphilis but that it happened to have been the pulmonary vessels which were diseased to a remarkable degree while the other organs of the body were only slightly diseased.

### *Discussion.*

DR. I. LEVIN said that if he had understood Dr. Brooks correctly he had here a case of localized arteriosclerosis, the etiology of which he ascribed to syphilis. This reminded him of cases of endarteritis of the lower extremities, also of a case of arteriosclerosis apparently with a secondary gangrene which some writers ascribe to syphilis as the chief etiological factor. Lately he thought the majority of writers denied this and said that while we do not know the etiology of a number of cases we can not point to syphilis as the main factor. He would like to ask Dr. Brooks what his real proof was, outside of the miscarriage, that this was syphilis. It seemed to him that the question of localized arterioscler-

osis was something which required an explanation; but he did not think that syphilis would explain it.

DR. T. C. JANEWAY asked Dr. Brooks if he did not think that the double mitral lesion with the resulting mechanical effects might have had something to do with the changes in the pulmonary system in this case.

DR. BROOKS said that he had tried to persuade himself that Dr. Janeway's explanation was correct, but that he had finally thrown it out because the changes were so very pronounced and so definitely limited to this one arterial system. The reason he had for calling the case syphilis was simply the reason most of us had when we do not know what else to call it. The character of the arteriosclerosis was more like that which ought to occur in syphilis than anything else he knew of. There were no gumma throughout the body, and nothing certainly syphilitic. The only reason was that it seemed the most probable explanation.

---

## THE REACTIVE POWER OF THE WHITE RAT TO TISSUE IMPLANTATION.

(A Preliminary Communication.)

ISAAC LEVIN, M.D.

The question, with what measure of success can we implant tissue or even whole organs of a highly organized animal into another part of the same individual or into another individual of the same species, is of greatest interest and importance in biology and medicine.

While every cell of an organism, no matter how highly differentiated, takes<sup>a</sup> part in the metabolic processes of nutrition, comparatively few cells retain the power of pro-



liferation. The same difference in the life energy of the cell takes place apparently when it is severed and implanted in a new place. The thyroid, pancreas, the whole kidney even, are being transplanted and are able to perform their normal functions for a certain time. On the other hand, we meet with far less success when we are implanting only pieces of an organ with the aim of causing the further proliferation of cells of the severed tissue.

Of all the pathological processes where proliferation of cells takes place, the hardest to comprehend as well as the most important, is the formation of a malignant new growth, and practically all the experiments with the implantation of tissue have been done in order to elucidate the genesis of malignant tumors.

The implantation of normal tissue, embryonic or adult, was usually done in order to prove a certain preconceived theory as to the factor inciting the cell proliferation in a new growth. In the great majority of experiments the results were negative. The implanted tissue usually becomes necrotic and is subsequently absorbed. The only exception is implanted epigermis which proliferates to some extent.

In 1901, I published the report of a series of experiments which I had undertaken on rabbits and dogs with the implantation of different tissues. With the exception of implanted epidermis my results were uniformly negative. The implanted tissue was always absorbed. Nichols reported, in 1905, a very similar set of experiments with the identical results.

A priori one would expect more success with the implantation of pieces of tumor than with normal tissue. Whatever the cause, tumor cells are certainly in a state of increased proliferation. But the implantation of tumor tissue in animals gave the same negative results. The successful

transplantation of the sarcoma of the genital organs of the dog can not be considered here, as the question whether this is a real tumor or an infectious growth similar to lues, is not yet settled.

In complete contrast with all these negative results stands the great success of the transplantation of sarcoma and carcinoma in white mice and rats. Since the first reports of positive grafting by Hanau, in 1889, an immense number of successful transplantations were done by Morau, Velich, Loeb, Jensen, Michaelis, Bashford, Ehrlich, Flexner, and others. This great difference between tissue implanted into any other animal which had so far been experimented upon, and pieces of a tumor of a white rat or mouse implanted into another animal of the same species, could be due only to one of two causes: Either the intrinsic power of limitless proliferation of a carcinoma or a sarcoma cell of a white rat or mouse is greater than that of any other cell, or else these animals react to tissue implantation, in a way different from other laboratory animals. The majority of the workers in this field seem to lean to the first explanation, and think even (Apolant), that the experiments on these animals have proven that the genesis of tumors must be explained by the intrinsic power of a tumor cell to limitless proliferation. Nevertheless there are facts in the results of these transplantations which seem to indicate that a great deal may be due to the reaction of the organism to the implantation.

In the first place, while a cell may act quantitatively differently in a different animal, it is hard to suppose that tumor cells so completely identical morphologically will be absorbed completely when implanted in any other animal, and will continue their growth and proliferation in a rat, and that still the difference will lie only in the cell itself. If in subsequent generations, implanted tumors become more

virulent, that is, proliferate more readily, the different behavior of the cell in the second host must be due to something which the cell acquired under the influence of the first host. The same is true with still greater force in cases of attenuation of the proliferating power of the cell, or the so-called immunity. The same holds true for the fact that the same tumor while growing well in a rat taken from Copenhagen does not grow at all in a rat from Berlin.

It may be interesting to note in this connection the following facts: A great deal of work was done with transplantation of human tumors on an animal and, as was to be expected *a priori*, with negative results. But Dagonet succeeded by implanting human carcinoma on a white rat in producing a real epithelial growth; and, what is very important from the standpoint of the influence of the host on implantations, the cells in the rat differed in size from the implanted human cells.

The hardest phenomenon to explain by the intrinsic power of the implanted tissue is the change of an implanted carcinoma into a sarcoma. Ehrlich thinks that in these cases the connective tissue stroma of the implanted tumor changes into sarcoma; but it would certainly be impossible to prove that this stroma is the implanted one and not the one formed by the host.

In view of all this it seems *a priori* possible that the white rat reacts differently to implantation, not only of tumor, but also of normal tissue; and to test this question experimentally this research was undertaken. I am implanting tissues of different organs into another place of the same rat or into other rats. While the work is not yet finished by far, and the detailed report of the experiments will be published later, some impressions have already been gained which seem of considerable interest.

Pieces of tissue of a size that would be absorbed in another animal very rapidly remain unabsorbed in the rat for a longer time, even when, as in the peritoneum, they do not become attached anywhere, but float like a foreign body. Much more frequently the pieces are either surrounded by a capsule consisting of an outer fibrous layer and an inner one, made up chiefly of round cells, or else the round cells invade and eat away as it were the implanted tissue. One is impressed with the great amount of organization going on around the implanted pieces. On the other hand, the pieces themselves seem to retain the cell structure much longer than is usual in other animals. The specimen shown under the first microscope was prepared from a piece of liver which was implanted ten days before the animal was killed, and the nuclei are still apparent. The same specimen shows the great quantity of round cells around the implanted piece.

Under the second microscope is shown a specimen from a very interesting case. A piece of skin which had previously been for a week in the peritoneum of a rat was implanted into the peritoneum of another rat. The animal was killed thirteen days later. At the autopsy there was found a tumor the size and shape of a nut, which was adherent to the anterior wall of the stomach and the lower surface of the liver, and moved freely with the liver. On incision it appeared to be a cyst containing a cheesy mass and pus; the wall was about one-eighth of an inch in thickness. As is seen under the microscope the wall of the cyst consists of an external fibrous part and an internal cellular one. Such a reactive cellular organization, whether against an implantation of foreign tissue or even against infection, one does not meet in other laboratory animals.

We know then that the implanted tumor of a rat proliferates and grows. We also know that extracts or filtrates

of tumors without cells do not produce any growth in another animal.

The aim of my work is to see whether the normal tissue of a rat implanted into another rat will itself grow or only incite the cells of the host to proliferation, and whether it can incite to proliferation only the connective tissue cells, or the epithelium also. Should the cells of a normal implanted tissue not proliferate, then I shall combine normal tissue with cell free extract of a tumor, and shall note whether in this combination a normal cell can be caused to proliferate in the host. All this will be the subject of my future communication.

In conclusion, I wish to express my gratitude to Prof. T. M. Prudden for the privilege of the laboratory. Prof. J. H. Larkin has aided me greatly in the microscopic part of the work, and I take pleasure in extending to him my thanks.

### *Discussion.*

Dr. JAMES EWING said that Dr. Levin had an important topic for experimental investigation. He would like to say as one of those who had read Dr. Levin's original paper on the subject that this was not entirely overlooked, at least not by a great many who were interested in the subject. The work which Dr. Levin had reported was, of course, as he had said, too incomplete to warrant any criticisms. The piece of tissue which he had shown was interesting, but only if it proved to be a tumor; and Dr. Levin had said that it was not a tumor. The work reminded Dr. Ewing of that reported at the Heidelberg conference by Lewin, who transplanted tumors from one animal to another and was able finally to get the recipient's tissues multiplying to such an extent that they were able



to continue growth in successive animals far more than is normal. Dr. Levin had brought out one new idea which Dr. Ewing had not heard expressed before, in regard to the transmissibility of tumors in certain animals. It has always been supposed that the differences in growth were due to differences in the cells; possibly, as Dr. Levin had suggested these were due to the reaction of the different animals to the transplanted cells. It seemed to him, however, that certain factors told against this theory. In the first place, there are few tumors of rats and mice which are transplantable. The vast majority of tumors in these animals behave as do tumors in other animals; that is, they resist transplantation. In regard to the lympho-sarcoma of dogs, of which Dr. Levin had spoken as not proven to be tumor, Dr. Ewing would like to refer him to the points which Dr. Beebe and he had put forward on this subject, and to invite him to visit the laboratory of the Cornell Medical College, to see the specimens on which their statements were based.

DR. J. H. LARKIN said that he had for some time had an opportunity of looking at some of Dr. Levin's work and noting his very careful technique, and had examined a great deal of tissue which he had implanted. While he did not concur with all of Dr. Levin's conclusions he would say that the suggestion which he had made in regard to the individual cells had something to it. In a number of transplantations which Dr. Levin had made of transplanted tissue the individual powers of that tissue to remain for long periods in other animals was very marked with white rats. In one of Dr. Levin's specimens of a case of transplantation of liver tissue, one could see very well the still persisting liver tissue in the center surrounded by its own leucocytes and again surrounded by a mass of connective tissue. That to Dr. Larkin's mind could mean only foreign body. The individual power of that piece of rat liver to persist in an-

other liver going on for that period of time, a power not found in other animals, was very suggestive.

---

## THE INFLUENCE OF INJECTED LEUCOCYTES UPON THE DEVELOPMENT OF A TUBERCULOUS LESION.

E. L. OPIE, M.D.

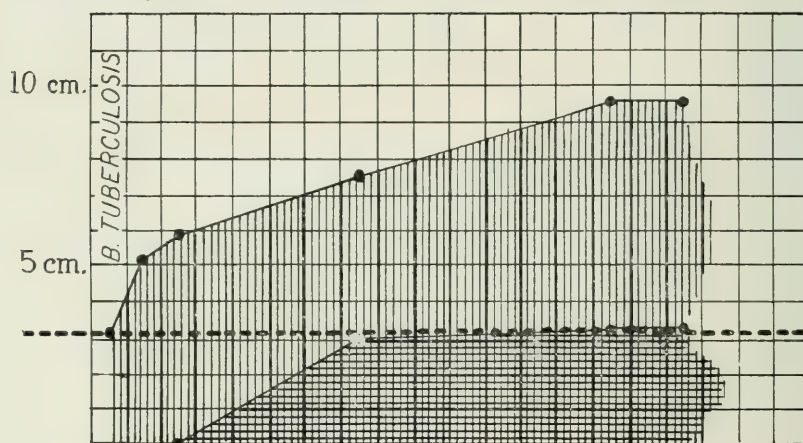
Dr. Eugene L. Opie presented some studies on the effect of injected leucocytes on the progress of a tuberculous lesion. For the purpose of the experiments the dog had been selected although this animal is naturally somewhat insusceptible to tuberculosis. Previous study had made Dr. Opie more familiar with the leucocytes of the dog than with those of other animals, and it had been found possible in this animal to obtain leucocytes in immense number.

Tuberculous pleurisy was induced in dogs by the injection of a suspension of tubercle bacilli into the pleural cavity. The lesion induced by the injection of 0.5 c.c of such a suspension is usually fatal in from five to six weeks. Occasionally, the disease runs a longer course of eight or more weeks. There is a rapid accumulation of fluid, which at death may amount to several hundred cubic centimeters, in the two cavities. The change is bilateral; injection into the right pleural cavity is followed by lesions on both sides of the chest. There are masses of tuberculous tissue, usually partly caseous, in the mediastinum and in the membranes below the pericardium. There are flat tuberculous nodules upon the pleural surfaces. There is tuberculosis of the mediastinal lymphatic glands with immense enlargement; and, finally, tuberculosis of the lymphatic glands elsewhere.

The lesion is especially adapted to a study of this kind because it can be followed during life by percussion of the dog's chest.

# XI

13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29



**Fig. 1.** Chart showing changes of dullness on percussion over the right pleural cavity into which has been injected a suspension of tuberculosis. Relative dullness, represented by light shading and absolute dullness, represented by dark shading, have been measured from the median line with the animal standing in its normal position. The dotted line represents the level of normal relative dullness caused by the projection of the heart to the right of the median line and measured at the time of inoculation.

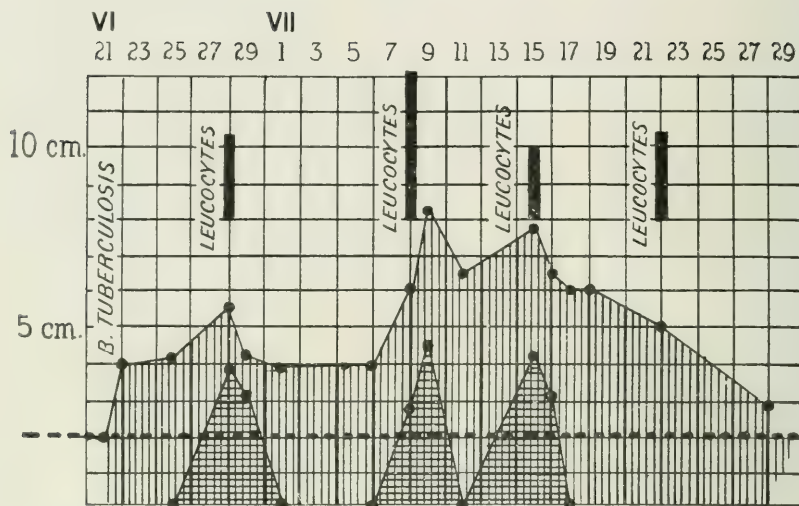
Series D, XXX.

Dr. Opie showed a diagram (Fig. 1), representing the changes of thoracic dullness which follow such an injection. The normal relative dullness caused by the heart usually extends two to three cm. to the right of the median line. As the result of the injection there is within twenty-four or forty-eight hours an increase of this relative dullness, and later perhaps absolute dullness marks its appearance. Occasionally, the absolute dullness which is caused by fluid within the pleural cavity may later disappear completely.

Relative dullness persists and autopsy shows that it is produced by masses of partially caseous tuberculous tissue. The presence or absence of absolute dullness doubtless depends upon the quantity of the fluid in relation to the size of the animal's chest. Since the lesion can be followed during life, it is especially satisfactory as a means of testing the effect of leucocytes injected into the chest.

Before passing to the effect of leucocytes upon this lesion, Dr. Opie described the effect of leucocytes injected into the normal pleural cavity. Leucocytes are obtained by injecting turpentine into the pleural cavity of a dog; they are washed; and the volumes injected represent almost solid cells. Injection of a small quantity (for example, 10 c. c.) of leucocytes into the pleural cavity of a normal dog causes an immediate increase of the relative and often of the absolute dullness in twenty-four hours; this increase of dullness is due to the presence of fluid. The reaction soon subsides; at the end of forty-eight hours the fluid is diminished in amount; and within two or three days the dullness has returned to normal. This change has been repeatedly produced in the same dog; and one animal which was killed after the fourth injection of from 10 to 12 c.c. of leucocytes showed a perfectly normal pleura.

When the leucocytes were injected into the pleural cavity of a dog in which tuberculous pleurisy had already developed, a fairly constant series of events followed. In all the experiments the injections of leucocytes were made only after it was possible to determine by percussion that a tuberculous pleurisy had developed, that is, about ten days or two weeks after the original injection of tubercle bacilli. At that time dullness over the dependent part of the right pleural cavity was considerably increased. Another diagram (Fig. 2), was shown, representing the condition of the animal's chest when leucocytes were injected



**Fig. 2.** Chart showing the effect of injected leucocytes upon dullness on percussion over the right pleural cavity which has been inoculated (21-VI-'07) with tuberculosis. The quantity of leucocytes injected is represented by the length of the short heavy lines, each space measuring 5 c. c. of washed cells. Series A, LIV.

into an animal whose thoracic dullness had been increased as the result of tuberculosis. At the end of seven days after inoculation, 10 c.c. of leucocytes were injected, and an immediate fall of relative dullness and disappearance of absolute dullness followed. The relative dullness, which did not return to the normal level was found to have increased after ten days, and a large quantity (22 c.c.) of leucocytes was introduced. Dullness did not diminish, but there was an increase of dullness followed by a fall and then quickly by another rise. It was interesting to note that a large quantity produced less diminution of dullness than a small quantity. Again introducing a small quantity of leucocytes there was a loss of dullness, and after the fourth injection there was still further loss.

The first series of experiments was performed at the



beginning of last summer and the phenomena described had been frequently repeated: the smaller quantities of leucocytes producing diminution of the dullness, occasionally with a slight preceding increase, and the larger quantities producing considerable increase, usually followed by a fall below the level before injection. Repeating the injections too close together, i. e., at intervals of less than a week, seemed to have an injurious effect.

The control animals showed a fairly uninterrupted increase of thoracic dullness. The injected animals showed a fall below the level present at the time the injections were started, and their area of dullness measured to the right of the mid-line approximated closely that present before injection of tubercle bacilli.

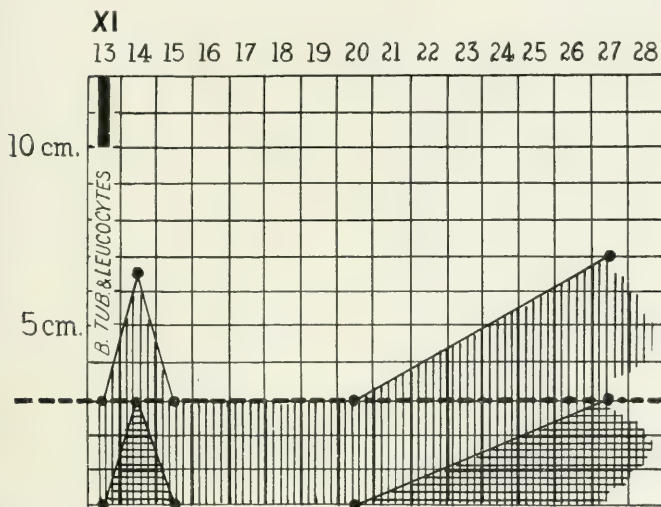
At the end of the summer, injection of leucocytes was stopped and the disease was allowed to take its course. The result of this series was as follows: Two controls died at the end of 34 and 37 days. An animal which received three injections died at the end of 57 days, and a second animal with three injections at the end of 68 days. An animal which received four injections died at the end of 89 days. Another animal which received four injections is still living at the end of six months and appears to be entirely well.

A second series of experiments is now in progress. It consists of seven animals, three of which are controls. Of the controls the character of the charted dullness is that already shown: usually a steady progress and perhaps death with accumulation of fluid. Of the three controls, two died at the end of five and six weeks respectively. The third control is still living with a considerably increased area of dullness. Of the four animals treated all have dullness corresponding to that before injection.

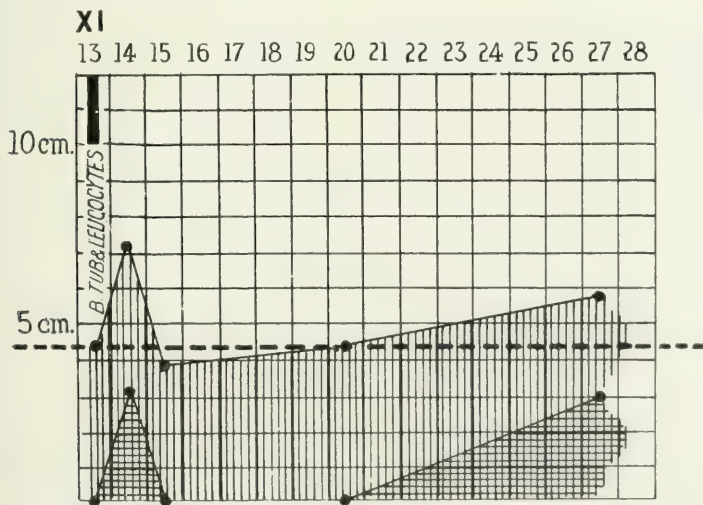
In a third series of experiments the results were contrary to those described. The control showed the course

exhibited by the other control animals, that is, a steady increase of both relative and absolute dullness. The second animal whose condition at the end of ten days was approximately that of the control received an injection of leucocytes which was followed by a disappearance of absolute, and marked fall of relative dullness. A second injection at the end of three days caused an increase of dullness. A third small injection was followed by a fall of dullness; but a very large injection (25 c.c.) was not followed by the usual fall; and this animal died at the end of 56 days. The control was then immediately killed and a comparison of the lesions was made. The animal receiving the tubercle bacilli without injection of cells showed advanced tuberculosis with large caseous masses in the mediastinum and in the membranes of either side of the pericardium. The animal receiving the injections of leucocytes showed chronic pleurisy with fibrous thickening of visceral and parietal pleurae. Compared with the control the tuberculous lesions were insignificant; there were small fibroid masses in each side of the pericardial cavity. Especially comparable were the mediastinal lymph glands; those in the animal which had received cells were small, whereas those in the control animal were several centimeters in diameter and were markedly caseous.

Since the foregoing experiments indicated that injected leucocytes retard the development of the tuberculous lesion, animals were inoculated with tubercle bacilli together with leucocytes, in the hope that the lesion might be entirely prevented. This hope was not realized; but the influence of leucocytes was marked. The immediate effect of the simultaneous injection of cells and tubercle bacilli was practically that of the injection of cells alone. There was an immediate increase of thoracic dullness followed by its complete disappearance at the end of forty-eight hours (Figs. 3 and 4). At first it was thought probable that tuberculosis would not develop, but at the end of about ten weeks dullness reappeared and it was obvious that the onset of tuberculosis had not been prevented. The animals which had received cells were given further injections and the dullness was reduced.



**Fig. 3.** Chart showing changes of dullness on percussion over right pleural cavity inoculated with a mixture of tuberculosis and leucocytes. Series D, XXVIII. Compare with Fig. 1, which represents the control animal of this series.



**Fig. 4.** Chart showing changes of dullness on percussion over right pleural cavity inoculated with mixture of tuberculosis and leucocytes. Series D, XXIX. Compare with Fig. 1, representing the control of this series.

In view of the fact that the lesion appeared to be retarded, a second series of two animals was prepared in the same way, and the result was identical. Inoculation of the control animal with tubercle bacilli alone was followed by a slow and continuous increase of relative dullness and the appearance of absolute dullness. The injection of cells plus tubercle bacilli was followed by a sharp rise of dullness with quick turn to normal; but at the end of two weeks abnormal dullness reappeared. The two animals were killed twenty-four hours after the appearance of the lesion in the animal receiving the leucocytes, and comparison of the lesions in the two animals was made. The animal which had received tubercle bacilli plus leucocytes showed a comparatively small amount of tuberculous tissue, and that which was present was almost wholly on the left side, the injection of tubercle bacilli and cells having been on the right. The animal receiving tubercle bacilli alone showed very large masses of tuberculous tissue on both sides of the chest. This animal exhibited many nodules upon the parietal pleura, whereas the animal receiving cells had an almost smooth pleural surface. There was anatomical as well as clinical evidence that the presence of leucocytes had retarded the development of the tuberculous lesion.

---

## LEUCOCYTES IN PROTEIN ABSORPTION.

P. A. LEVENE, M.D.

The mechanism of protein absorption still remains insufficiently explained. The greatest difficulty in solving the problem is found in the fact that proteins of the tissues and those of the food differ little in their chemical composition. In recent years a number of proteins have been dis-

covered which differ in their composition from the usual tissue proteins. However, after feeding animals on these substances it was impossible to detect them either in the blood or in the other tissues.

It has also been established in recent years that in the course of digestion proteins undergo a very definite alteration in their composition. Proteins consist of a chain of amino acids linked in such order that some are removed from the molecule by the action of enzymes with less difficulty than the other acids. Thus, leucin and tyrosin are generally the first amino acids split off on protein digestion; glutaminic acid remains the longest combined into a complex molecule. A digested protein, therefore, differs from the native substance in that it contains a lower proportion of leucin and tyrosin, and a higher proportion of glutaminic acid.

In the course of a study of the composition of nucleoproteins of various organs, Dr. Mandel and Dr. Levene had made the observation that the nucleoproteid of the spleen contained a considerably higher proportion of glutaminic acid (25 per cent.) and a lower proportion of leucin, than any other animal protein, thus resembling the proteins which have undergone to some extent the process of digestion. On the ground of this observation it seemed suggested that the leucocytes derive some of their proteins from the intestinal tract, and thus serve as transporters of the food proteins.

#### *Discussion.*

DR. JAMES EWING asked Dr. Levene whether he thought that the fact that glutaminic acid remained longest in the cell undergoing digestion would explain the high proportion of glutaminic acid in the protein of tumors which are supposed to autolyze more rapidly than other tissues.



DR. LEVENE asked whether it was known that the glutaminic acid in tumors was in high proportion.

DR. EWING said that certain examination had been reported in which a high proportion of glutaminic acid and a low proportion of leucin had been found in tumors, and it was thought that this was characteristic of tumor tissues. He had thought that, in view of Dr. Levene's results, an active autolysis of the tumor might explain the persistence of glutaminic acid.

DR. LEVENE thought it very possible that this might be so.

---

## SPORULATION OF THE GROUP OF BACILLUS AEROGENES CAPSULATUS,

HIDEYO NOGUCHI, M.D.

*Bacillus aerogenes capsulatus* (Welch) is noted for its persistent refusal to form spores when cultivated in most of the artificial nutrient media. Dunham first succeeded in inducing its sporulation in a coagulated serum medium, in which the spores were seen to form in the condensed water. Without touching the question whether *B. aerogenes capsulatus* of Welch and Nuttall is identical with *B. phlegmonis emphysematosae* of Fraenkel, on the one hand, and *Granulobacillus saccharobutyricus immobilis* of Grassberger and Schattenfroh, on the other, we have in them in common a persistent absence of sporulation in usual culture media, notwithstanding the fact that these strains had been primarily, and can always be, isolated by the means which necessarily indicate the occurrence of sporulation under natural circumstances. Fraenkel, as well as Hitchmann and

Lindenthal failed to induce sporulation of Fraenkel's bacillus; while Grassberger and Schattenfroh also state that it is difficult to obtain uniform sporulation of their immobile butyric acid bacillus in ordinary nutrient media.

In his exhaustive and extensive researches on the anaerobic flora of the intestine, both of human subjects and of animals, Herter observed occasions where sporulation of the gas bacillus was undeniably demonstrated in the intestinal contents, especially in the feces of carnivorous animals. Still, he recognizes the inconstancy of sporulation of this bacillus even in the feces, and agrees that it seldom sporulates in usual culture media,

Grassberger and Schattenfroh give a method by which they were able to induce uniform sporulation of their immobile butyric acid bacillus. Their method consists in adding varying amounts of alkali to 0.1 per cent. starch agar, usually 5 to 20 drops of N/5 NaOH solution to 10 c.c. of the starch agar. Their purpose in preparing many tubes of varying alkalinity was to get the optimum alkaline reaction for the sporulation. This method seems, however, not to have received much attention from those who are working in similar lines, and sporulation of the group of *B. aerogenes capsulatus* remains to-day still an uncontrollable factor.

While working with several strains of the group of *B. aerogenes capsulatus*, I had occasion to observe sporulation of these strains when cultivated in certain media, and thought it advisable to communicate the results briefly. The strains with which I worked included *B. aerogenes capsulatus* (for which I am under deep obligation to Prof. Theobald Smith), *B. Saccharobutyricus immobilis*, isolated by myself from market milk, and two more strains of *B. aerogenes capsulatus* isolated from human feces. When cultivated in usual fluid or solid media, none of them formed spores. The strain obtained from Professor Smith occasion-

ally formed spores in sugar-free media, while the other failed to sporulate under the same conditions. It may be stated that the reaction of the media employed had an alkalinity corresponding to about N/50 to N/75 NaOH, that is, that much alkali was required to make it neutral to litmus paper, although the alkalinity above stated did not react to phenolphthalein.

The results which I obtained with these organisms may be summarized as follows:

Using the sugar-free bouillon with alkalinity corresponding to N/50 to N/75 NaOH as the basic medium, I added various kinds of carbohydrates in the ratio of 1 per cent., and inoculated each series. After cultivating them for from three to seven days, anaerobically at 37° C., they were examined microscopically. It developed that the strains cultivated in the media containing 1 per cent. amygdalin, salicin or mannit formed spores in large number, many of which were seen to be in the free state. On the other hand, no sporulation took place in the media containing glucose, lactose, maltose, glycogen, saccharose, dextrin, and levulose, in 1 per cent. Likewise, no sporulation was obtained in milk. In control tubes some spores were seen to be present with the strain of Professor Smith, but far less than in the media containing amygdalin, salicin, or mannit. It was also noticed that the substances in the presence of which no sporulation occurred, were fermented by these strains, and the reaction of the cultures became very acid; while the glucosides and mannit remained almost unattacked, or were fermented to only a slight degree, the violet tint being little changed (litmus media). Exactly the same results were obtained when, instead of sugar-free bouillon, Hiss' serum-water was employed as the basic medium. With Hiss' medium, 1 per cent. sorbit, dulcit and inulin were also tried, and found to behave in a manner similar to the glucosides

and mannit in enabling the organisms to sporulate. It was noticed later, however, that even in these media some strains—especially that of Professor Smith—sporulate more easily than the others.

### *Discussion.*

DR. CHARLES NORRIS said that he had always felt that there were a large number of organisms included under the name of *aerogenes capsulatus*. While working in the laboratory of the College of Physicians and Surgeons at the time Dr. Dunham's paper appeared, he had experimented with a number of cultures which he had on hand, using serum-water and Loeffler's, and had been unable to convince himself that the species which he had, did form spores. There was evidently great variation also in regard to gas formation. With many species of *aerogenes* one did not get the swelling of the rabbit's body as quickly as with others. With some of the cultures he had obtained one could recover bacilli from the frothy fluid as it exuded from the nose at room temperature, within three or four hours.

---

## ACUTE CALCIFICATION OF THE ARTERIES IN A CAT WITH TRANSPLANTED KIDNEYS.

ALEXIS CARREL, M.D.

Dr. Alexis Carrel showed specimens of acute calcification of the arteries in a cat whose kidneys had been removed and replaced by kidneys from another cat. This calcification was of a very peculiar kind. The clinical history of the cat was very simple. The animal was a young adult, in perfect health. Before beginning the experiment

the cat's urine was examined; the quantity was found to be normal, and there was no albumin. Both kidneys were then removed and immediately replaced by both kidneys from another cat. After this operation the life of the cat went on just the same as before. The quantity of urine was undiminished; the composition was practically the same; and the animal was apparently in good health. Examination of the urine showed that there was no albumin; and the size of the kidneys was entirely normal.

Fifteen days after the operation the animal was considered to be completely recovered and was allowed to go about the laboratory freely. At that time it took a great deal of exercise. After two days of exercise, it was found that both kidneys were very much enlarged. At the same time the quantity of urine was increased, and contained an enormous amount of albumin. Laparotomy was performed and the kidneys were found to be very much enlarged. The circulation in the renal vessels was perfectly normal. There was no congestion of the kidney; and after incision of the capsule of the kidney clear fluid and blood escaped. There was at the same time edema of the connective tissue. The wound was closed and during the days following the operation the quantity of albumin diminished. The size of the kidneys also diminished progressively; but about twenty-five days after the operation the animal appeared to be sick, refused to eat, and died thirty-six days after the operation.

A post-mortem examination was performed, and on opening the abdominal cavity it was found that both kidneys were of normal size, color, and consistency, though they had appeared slightly enlarged. On section they were apparently normal. The ureter and bladder, too, were normal. The only abnormal feature was that the wall of the abdominal aorta was exceedingly hard, amounting to complete



calcification. The mesenteric artery, too, was calcified. Examination of the other organs did not show any marked change. Sections of the carotid and femoral arteries showed the same lesion. The arteries were completely calcified; the walls were of the consistency of a thin glass tube, and could be broken the same as glass. Examination of the organs of the thoracic cavity showed exceedingly marked change. In the aorta it was possible to see areas of calcification. Examination of the specimen showed that there was a deposit of salt in the adventitia which extended into the media. The lesion was more localized in some arteries and the internal part was not in normal condition, but the lesion was much less marked. In the carotid artery the lesions were localized in the external part and practically all the media was completely destroyed. The kidneys were in good condition.

It would be interesting to explain the course of this very marked change, but at the present time one could only draw hypotheses. It was not possible to ascertain the nature or cause of the modification of the metabolism which produced this great anatomical change. In order to try to reproduce the lesion, Dr. Carrel had begun some experiments. For instance, by denudation of the kidneys and suppression of the circulation for a little while it was hoped that some lesion would occur which would perhaps produce a lesion of the vessels similar to lesions found in this cat. He had also tried adding two suprarenals to a cat in order to produce some modification of the arterial system; but at the present time it was certainly very difficult to explain the cause of the anatomical lesion found in this animal.

### *Discussion.*

DR. A. MAYER asked whether control experiment had been made. It would also be interesting to know whether

the cat from which the kidneys were transplanted was an older cat than the one receiving the kidneys, in which one might have conditions of calcification. He would also like to know whether or not control experiments had been made with cats of the same age, in which case some other lesions might perhaps be noted.

DR. HORST OERTEL asked whether any changes had been found in the vasa vasorum or in the bones. This seemed interesting to him in view of the fact that these changes were observed in the adventitia, not in the intima, as in true arteriosclerotic calcification. Inasmuch as there must have been a large demand for calcium within a comparatively short time, it would also be instructive to know something of the condition of the bone.

DR. P. A. LEVENE asked whether or not observations have been made on the conditions of the blood vessels of animals which had received injections of tissue emulsions.

DR. A. W. WADSWORTH said that he recalled autopsying animals after prolonged immunization, and seeing in two or three such animals marked calcification of the arterial system extending from the heart through into the abdomen. He had, of course, made no study of the calcification as he was simply studying the immunity of these animals and had not determined whether the calcification was due to age or not; but he had autopsied many rabbits and had seen this peculiar degeneration in no other animals. The animals were inoculated subcutaneously and intravenously. Other observers, Dr. Wadsworth thought, had obtained arterial lesions experimentally in animals as the result of bacterial inoculation.

DR. CARREL said that the cat which underwent the transplantation was about one year old. At the time of the transplantation it was necessary, of course, to make a dissection of the abdominal aorta and the vessels of the kidney,

and these were held between the fingers; so that it was easy to say that they were absolutely elastic. The second cat, the one which gave the kidneys, was about two years old and was in very good condition. For the transplantation it was again necessary to make an extensive dissection of the aorta and it was easy to see the condition of the vessels. This cat had a perfectly normal aorta without any calcification. In the other experiments of transplantation of the kidneys, Dr. Carrel did not observe any kind of calcification. It might be that some lesion of the organ occurred which was followed by the special trouble of metabolism which produced calcification. No definite study of the small vessels had been made. The vessels of the spleen and liver showed no calcification of the walls, though there might be some slight infiltration, especially of the splenic artery.

---

## METAPLASIA AND LYMPHATIC METASTASIS OF A RAT TUMOR.

J. W. JOBLING, M.D.

I wish to speak briefly of a tumor of the rat that has been under study and transplantation by Dr. Flexner and myself for more than two years. The tumor originated in the seminal vesicle of a rat and has now been carried through about twelve generations. It is clear that the tumor is one that will probably remain indefinitely transplantable. We have not attempted to shorten the period between the generations, which would have been easily possible, in order to secure a larger number of them. The tumor is relatively a slow-growing one: to reach the size of a walnut takes about three months, which is also about

the average length of time required to produce internal metastases and bring about spontaneous death.

The primary tumor was of mixed character but it approached the connective tissue rather than the organoid type. It was, however, different from the ordinary sarcomata since while it was composed mainly of spindle cells there were associated with these, cells of an epithelioid or endothelioid character. The latter cells were even at times arranged into tubuli with bibullated connective tissue delimitation.

In the course of further transplantation these larger cells tended, in certain series, to increase in number at the expense of the spindle cells until in the fifth generation they became dominant. At the present time the tumor of the eleventh generation is composed of an adenomatous growth which bears little or no resemblance to the original tumor.

This change is not confined to the microscopic appearances alone. The smaller tumors of the original type were usually round and so firm that it was almost impossible to pick one up with plain tissue forceps. The tumor at the present time is of softer consistence and much more readily broken up.

Since one series of transplantations has undergone this adenomatous change and the other has not, and as both forms of the tumor are still growing in different rats, it is easy to distinguish them in the living animals by means of their hardness.

The tumor of the eleventh generation which is most greatly altered shows spindle cells only at the advancing edge, while the body of the tumor is composed of a dense fibrous stroma upon and in the regular spaces of which the epithelioid cells are implanted and at times in an imbricated manner. Larger spaces suggesting cystic dilatations,

smaller alveoli suggesting acini, and outgrowths suggesting papilloma all occur. Mitotic figures are fairly common.

Coincident with this structural change a new class of metastases has appeared. Previous to the fifth generation and before the alteration in the tumor being considered took place, lung and kidney metastases were frequent, but no lymphatic metastasis was encountered. Beginning with the fifth generation lymphatic metastases have become more and more frequent, until now, in the eleventh generation, though only a few of the animals of the series have died, yet the number of rats showing lymphatic nodules is much larger than ever before.

The adenomatous tumor grows faster than the tumors of the original type. Tumors of the twelfth generation (adenomatous) are at the end of three weeks as large as the tumors of the older type were at the end of four to five weeks.

---

## THE RATIO BETWEEN THE WEIGHT OF THE HEART AND THE WEIGHT OF THE BODY IN ANIMALS.

DON R. JOSEPH, M.D.

(From the Department of Physiology and Pharmacology of the Rockefeller  
Institute for Medical Research)

Dr. Don R. Joseph said that there was a certain average ratio of weight between heart and body which could be considered normal. For the human being, tables had been compiled showing the average weight at different ages (1). During the past three months he had studied

(1) See *Vierordt*: Anatomische, Physiologische und Physikalische Daten und Tabellen. 1906.



the relation between the heart weight and the body weight of animals used in the laboratory. The weight of each animal was taken before any operation was begun, and after death the heart was removed, emptied of blood, and weighed. The animals studied were dogs, cats and rabbits. By the term "ratio of heart weight to body weight" was meant the number of *grams* of heart tissue to every *kilo-gram* of body weight.

According to Vierordt's tables, in man, the younger the individual the higher the ratio between the weight of the heart and the weight of the body. In Dr. Joseph's series, the ages of the animals were, of course, indefinite. It was found that the average ratio of each species was quite constant for that species. As an example of this, a dog whose body weight had not been previously determined was operated upon, and after death, from the weight of the heart the total body weight was estimated to be 12 kilos 450 grams. The actual weight of the body was found to be 12 kilos 100 grams.

Species	Sex	Number of Cases	Average Heart Weight	Average Ratio
Human <sup>1</sup>	Male	30	301	4.60
	Female	27	260	—
Dog	Male	28	62	7.50
	Female	25	42	7.64
Cat	Male	10	13	4.65
	Female	15	12	4.58
Rabbit	Male	21	4	2.70
	Female	36	4	2.88

(1) Taken from Vierordt's Tables.

From the table it would be seen that the ratio in human beings and in cats was about the same, that in dogs much higher, and that in rabbits much lower. An explanation of this condition in the rabbit might be that the stomach and cecum of this animal have an enormous capacity, so that if the weight were taken after a full meal the ratio would, of course, be low. A ratio in which the stomach and cecum contents were excluded would probably be nearer that found in other animals. In the case of the rabbit there was also another variation. Whereas in man, dogs, and cats, the male ratio was much higher, in rabbits, the female was the greater. This was possibly due to the fact that the female rabbit is less active than the male, and, therefore, the contents of the cecum and stomach are greater.

Dr. Joseph thought that his present figures indicated that the relation of the weight of the heart to that of the body follows the law, not of a *direct* but of an *inverse* proportion, or, in other words, the ratio diminishes as the body weight increases. This law might be connected with the well known observation that small animals have high pulse rates, or, in other words, the smaller the animal the higher the pulse rate. Could not this rapid heart beat be the cause of a physiological hypertrophy?

---

## DEMONSTRATION OF TREPONEMA PALLIDUM WITH THE DARK-FIELD ILLUMINATION MICROSCOPE.

SIMON FLENNER, M.D.

I am glad to have the opportunity of exhibiting to the Pathological Society this microscope, made by Reichert of Vienna, which will, I think, become of value in certain kinds of study, and I am particularly glad to be able to exhibit

living specimens of *Treponema pallidum* with it. All doubt and discussion regarding the microorganismal nature of the pallidum have now been removed, thanks to this ready method of observing with ease and distinctness its changing form and motions.

The specimens which you will see were obtained from an unopened papule of the tongue from a patient who began to show secondary lesions of syphilis five weeks ago. When she reported at the City Hospital, a lesion, probably the primary one, was found on the genitals and she exhibited a general maculo-papular eruption. As you will observe, the spiral organisms, which have the character of *T. pallidum*, are quite numerous. Every field of the microscope contains one or more of them, and they are actively mobile.

On account of the large number of members present, you cannot study the individual organism closely enough to make out all its motions. The motions which are immediately evident are a side to side and a forward and backward one, that are constant and are probably chiefly Brownian in nature. I have observed these motions after the slides have been in the refrigerator for several days and they were almost as active as at present. These oscillations give a dancing appearance to the organism. But in addition to these, many of you will see the spirals revolve on their long axis, or execute sharp contractions, or bend their bodies so as to bring the opposed ends together to form a circle, or move slowly forward across the field of the microscope by turning or by a series of contractions.

The activity of the spirals is greatest immediately after being taken from the lesion. At this time, it is sometimes difficult to follow the evolutions—turnings, bendings, contractions—through which they pass. If at this period two individuals come together, they are apt to twine one about the other to form those combinations which have been mis-

taken for evidences of longitudinal division, etc. The entwined individuals may be seen to unwind and to go off across the field of the microscope. The mobility lessens after an hour or two or even after a less time; but a certain grade of mobility can be discerned some hours after the preparation has been made provided the evaporation of the fluid has been prevented.

Slides kept in the refrigerator continue to show the pallidum for a week or longer, but the refraction is altered in the kept specimens and they show less brilliantly than in the fresh state. The specimens keep poorly at the room temperature because of the development of saprophytic bacteria which tend to obscure or destroy the pallidum.

I have studied local syphilitic lesions—chancre and papillary lesions of the skin and mucous membranes—and have had no difficulty in finding the pallidum in them. The rapidity with which they can be demonstrated, often almost at once after placing the slide under the microscope, is very striking and will make this method of examination of great diagnostic value. The method is particularly well-adapted for dispensary and office practice. I have found rather larger numbers of the pallidum in papules of the mouth and a papule of the penis than in primary lesions. But I have not found it difficult to demonstrate the spirals in primary lesions. Since the apparatus has been in use I have had no opportunity to examine lymphatic gland juice or tissues from syphilitic fetuses.

A primary lesion on the eyebrow of a macac monkey, which was of a few days duration and not ulcerated, showed the pallidum in fair numbers and in a very active condition and it was indistinguishable from the organisms from human beings.

In preparing preparations for the microscope it is desirable to secure lymph with as little admixture of blood as

possible. The fewer the large morphological elements in the preparation, the clearer will the field be and the easier the pallidum will be found. Air bubbles should be sedulously avoided; and it should be remembered that many minute, ultramicroscopic particles not visible in the field of the ordinary microscope become visible in the field of the dark-field microscope.

---

## DEMONSTRATION OF THE SPIRILLUM OF TICK FEVER.

B. T. TERRY, M.D.

The second organism demonstrated, the *Spirillum* of Tick Fever, was obtained originally by Dr. Robert Koch in East Africa from a case of human relapsing fever. This African fever is quite distinct from the European relapsing fever. From the latter it differs, as a rule, by shorter attacks and relapses, by very irregular intervals between relapses (these varying from one day to three weeks), and by the greater number of possible relapses (eleven have been noted), even at the height of the infection.

By immunity experiments, Fraenkel has recently shown that the spirillum causing relapsing fever in East Africa differs specifically from that causing a similar disease in West Africa. For the former he proposes the name "*Spirillum* of Tick Fever," retaining the older name "*Spirochaeta duttoni*" for the West African disease. Both of the African organisms are transmitted from patient to patient by the bite of a tick, *Ornithodoros moubata*. Some of the eggs of infected ticks are infected, and the young, hatched from infected eggs, are capable of transmitting the



disease. The organism of tick fever is larger than *Sp. pallidum*, its undulations are less regular, its movements are more active, and, under the dark-field microscope it makes a more brilliant picture.

---

## A CASE OF TUBERCULOSIS OF THE DUCTUS THORACICUS.

RICHARD WEIL, M.D.

The specimen presented was taken at autopsy from a case of acute general miliary tuberculosis. All the organs usually involved in these cases showed the typical lesions, a very great number of very early miliary tubercles. The lungs showed no old lesions with the exception of an apical scar. The bronchial lymph nodes were considerably enlarged and caseous. The thoracic duct showed a number of tubercles protruding into the lumen of the duct, considerably larger than any of the tubercles in the organs, which were all very small. In addition, there were distinct ulcerations along the course of the duct. The lesions in the duct were in an intermediary stage between the old lesions in the bronchial lymph nodes and the general miliary tuberculosis. Sections of the duct were demonstrated, showing caseous masses containing numerous tubercle bacilli, projecting into the lumen of the duct.

As far as the literature was concerned, Dr. Weil said that the Phipps autopsy records show no mention of the lesion. Longcope in his studies devoted special attention to the point and in a series of thirty autopsies examined the thoracic duct very carefully. In ten he found that he could demonstrate caseous lesions in the duct. In a few other

cases he found miliary tubercles which were of the same age as the miliary tubercles elsewhere in the body, and therefore did not count, as according to Weigert's law the lesions in the duct must be much older in order to be considered primary.

---

## A CASE OF DOUBLE PYELITIS, URETERITIS, AND CYSTITIS CYSTICA.

O. H. SCHULTZE, M.D.

Dr. O. H. Schultze presented a case of double pyelitis, ureteritis and cystitis cystica, with a large renal calculus on the left side, the organs having been obtained from a male adult, about fifty years of age, a patient at the Metropolitan Hospital. The lesions described had practically nothing to do with the patient's death, as there was also a very large dilated heart, insufficiency of the mitral valve and very extensive chronic tuberculosis with the formation of cavities and considerable fibroid connective tissue. The bladder showed in the trigone a large number of cysts, varying in size from a fraction of a millimeter to several millimeters in diameter. Both ureters also showed these cysts, some quite large near the opening of the bladder. The pelvis of the right kidney showed several cysts, some containing pale fluid and others yellowish brown fluid. The left kidney had a large stone filling the entire pelvis and the calyces. There were also several cysts in the pelvis.

The subject of ureteritis cystica had been so well covered by Dr. Stow in his paper before the Society (February, 1907) that Dr. Schultze thought it unnecessary to go into it. Regarding the question of chronic irritation of one kind or

another as a cause, Dr. Schultze said that in a case such as the one shown one might jump at the conclusion that the stone had something to do with the lesion, but, on the other hand, no stone was found on the right side, which also contained cysts. Dr. Schultze had seen several cases of the affection in the bladder, but this was the first case he had seen of the lesion in the pelvis of the kidney. Besides the points already mentioned there were also a few purulent foci in one kidney.

---

### A CASE OF DIPHTHERITIC LARYNGITIS, TRACHEITIS AND BRONCHITIS.

THOMAS FLOURNOY, M.D.

The chief interest in this case was in the examination of the gross specimen, as the extent of the membrane formation was rather unusual. The case had come to autopsy a few days ago. The patient was a man who had been sick for about one week. He was in the hospital only about twenty-four hours before death. He had had some bleeding from the nose before he died, but the heart action had been good. The membrane extended from the epiglottis to the finer bronchi.

---

### A CASE OF ENDARTERITIS OBLITERANS.

I. LEVIN, M.D.

Before demonstrating the specimens, I shall give a brief clinical history of the case. The patient, a man, aged thirty-five years, came to my office complaining of severe pain in the right big toe and leg which had continued for the last eight weeks. On examination, the patient was found to be

poorly nourished and anemic. The right leg and foot were paler than the left, and were cold and clammy to the touch. There was a small gangrenous spot on the inner surface of the nail phalanx of the big toe. No pulsation could be felt in the arteria dorsalis pedis or tibialis postica; there was faint pulsation at the upper section of the popliteal. Otherwise, the patient had no organic disease, no heart lesion, tuberculosis, Bright's disease, diabetes, or congenital or acquired syphilis, and no indication of general arteriosclerosis. I made a diagnosis of spontaneous gangrene due to endarteritis obliterans, and devised amputation at the knee joint. At the urgent request of the patient, however, I first amputated the toe. Gangrene developed at the line of incision and two weeks later I amputated the leg at the knee joint. The patient made an uneventful recovery.

On gross examination all the arteries of the leg appeared very hard and unelastic. Microscopical sections were taken from the upper part of the tibial artery as well as from the stump of the toe. I take here the opportunity to thank Dr. J. H. Larkin for his help in the preparation of these specimens.

Study of the specimens reveals the following conditions: The walls of all the arteries as well as of the veins are greatly thickened, due mainly to a proliferating hypertrophy of the middle muscular coat. The intima is only occasionally thickened, and then in a comparatively small degree. The lumen of the vessels, while always diminished, is completely occluded only in the very small branches of the arteries, both the tibialis and dorsalis pedis being patent. In the arteries no thrombus formation could be detected, but most of the veins contain organized or unorganized thrombi. There was also noticed connective tissue formation in the nerve sheaths and intrafascicular bands of the nerves.

In considering cases of this kind there are two questions

presented for solution: First, is the etiological factor which produces a local lesion in the blood vessels much severer in extent than any found in cases of general arteriosclerosis? Second, what is the reason that in some of these cases gangrene forms comparatively soon, as in my case, while other cases continue for years as conditions of so-called "intermittent claudication" without any tendency to gangrene?

As to the first question, some investigators consider endarteritis obliterans a local manifestation of some general infection like syphilis, or intoxication like tobacco. Others maintain that the primary etiological factor is a diseased condition of the vasomotor nerves. Neither morphological nor experimental study can determine this question. A lesion of the arterial wall looks very much the same whether it is caused by syphilis, diabetes, or experimental injection of adrenalin or tobacco. But the clinical examination of these cases shows that the best explanation of these conditions is that they are due to a primary lesion of the vasomotor nerves. The main clinical symptoms of the disease are vasomotor disturbances and pain. The same symptoms occur in a group of cases faultily called Raynaud's disease. While in the latter disease all the symptoms, as well as gangrene, are due to ischemia caused by a nervous spasm of the muscularis, in endarteritis obliterans the constant irritation of the vasomotor nerves goes a step further and causes hypertrophy of the muscularis and subsequent proliferation of the other tissues of the walls of the blood vessels.

Gangrene or local death of tissue is caused by a complete loss of blood supply. If in two cases of endarteritis obliterans there was gangrene in one and not in the other, apparently the explanation would be that in the latter case the general circulation was strong enough to overcome the increased local obstruction, which it could not do in the former. The venous thrombi of my case show that the circulation in the leg had been very slow and inadequate.



*Discussion.*

DR. CHARLES NORRIS asked what the nationality of the patient was.

DR. LEVIN said that he had neglected to state that the patient was a Russian Hebrew, as were all of these patients, with the exception of some cases reported from Japan.

DR. JAMES EWING said that he had recently had an opportunity of examining an advanced case of this kind, occurring in the New York Hospital, for *Sp. pallida*, by the Levaditi method, and though he had made quite a number of sections and was satisfied that the stain was successfully performed, he had been entirely unable to find any traces of *Sp. pallida*.

DR. J. H. LARKIN said that Dr. Levin had turned over to him the amputated leg, from which he had dissected all the blood vessels. At the time he had first seen it he could not for a moment conceive why he would amputate a leg below the knee for practically an insignificant amount of necrosis involving only the great toe; but careful dissection of all the blood vessels from the distal part of the leg showed a very marked disease of the posterior tibial artery and of the smaller arteries dissected out at that time. At first glance the microscopical sections which had been made of all the arteries available on dissection showed the advantage of such a surgical procedure. The arteries showed perhaps one of the most marked cases of endarteritis that one could possibly see from a case with an almost insignificant amount of gangrene occurring only around the nail of the toe. Inflammation of the nerves, perineurium and endoneurium, in this particular case, both in the upper part of the amputated stump and in the neighborhood of the gangrenous area is most marked. The cellular endophlebitis around the veins and the marked parietal thrombi in the veins were most sig-

nificant. Dr. Larkin thought that from the microscopical sections, the magnitude of the operation and the insignificance of the change for which the operation was done, this might be considered a notable case, showing the advisability of such a procedure.

DR. HORST OERTEL asked what this case was to be considered. According to Dr. Levin the process consisted of hypertrophy of the media, and according to Dr. Larkin it was endarteritis.

DR. LEVIN said that these cases were called endarteritis obliterans; why, he did not know. Apparently in a majority of the cases the affection is only in the media or the muscularis. Some authors have reported cases where thrombi did form in the arteries, and these would probably be more properly called endarteritis. To answer the question touched upon by Dr. Larkin, Dr. Levin said that he had not intended to say anything in regard to surgery, but since the question, why amputate a leg when the lesion is only in the toe, had been raised, he would say that it was known clinically that in these cases nothing short of amputation below the knee will stop the gangrenous process. During the course of this operation no bleeding took place.

DR. LARKIN said that when Dr. Oertel looked at the lesion under the microscope he would find, not only an endarteritis, but also an hypertrophy of the media and the muscularis. Another interesting thing in connection with this case was the presence of organized thrombi in the veins in connection with the arteries. He thought that with the slow circulation occurring in the arteries and veins there was probably partial organization and canalization in the various vessels. He considered the case a combined endarteritis and fibrous formation in the musculature.

DR. T. C. JANEWAY asked whether Dr. Larkin and Dr. Levin were dealing with the same arteries when they spoke

of endarteritis and of hypertrophy of the media. If they were dealing with the larger arteries central to the obstruction, hypertrophy of the media was the process which would be expected. Dr. Carrel, in his studies at the Rockefeller Institute on the effects of suturing arteries into veins, had shown that the physiological effect of lowered pressure in the blood vessels was apparently to produce a regressive change in the muscular coat with increase in the size of the lumen. On the other hand, arteries central to a narrowing show extreme thickening with diminution of the lumen. Endarteritis obliterans as a true inflammatory disease of the arteries had nothing to do with these changes. Dr. Janeway also took issue with Dr. Levin's statement that in all these cases the gangrene goes up to the knee. One sees a proportion of the cases where the gangrene is demarcated. These cases are extremely interesting clinically, inasmuch as they present every gradation from the old people with simple cramps in the leg at night, because when they sleep the velocity of the blood flow is not sufficient to keep up the peripheral circulation, to the cases of true intermittent claudication on walking, and Raynaud's disease. Whether in these cases the nervous influence produces the thickening of the vessels and the gangrene, or whether the thickening of the vessels is the cause of the pain, is apparently unsolved.

DR. LARKIN said that from his dissection of the arteries in this case he thought that this was practically the smallest popliteal artery he had ever seen. Microscopical examination of the artery at the amputated stump showed a marvellous diminution in size. He was sure that the process was a pathological and not a physiological hypertrophy.

DR. JANEWAY asked whether Dr. Larkin meant a diminution in the lumen or in the wall of the artery.

DR. LARKIN said that he meant a diminution, not only of the lumen, but of all the coats of the artery.

DR. HARLOW BROOKS asked whether the term hypertrophy of the muscular coat had been chosen with due deliberation.

DR. LARKIN said that he had not had the opportunity of putting through all the arteries to decide upon the exact amount of connective tissue which occurred in the musculature, but he thought one might gain a good idea from the sections of the amount of hypertrophy of the muscle.

DR. OERTEL said that if he understood correctly the process was then simply an endarteritis obliterans with some changes in the media?

DR. F. S. MANDLEBAUM said that he had not intended to say anything at this time, but inasmuch as he had been called upon he would like to say that Dr. Buerger had been working on this subject for some time in the laboratory of the Mt. Sinai Hospital. He had had eight cases similar to the one reported. He had concluded that instead of being endarteritis, all of these cases were due to the formation of thrombi in the vessels. These showed more or less canalization; but it was apparent that the process is not a disease of the intima of the vessels at all, but is entirely due to thrombi and secondary changes. Dr. Buerger was about to publish his series of cases at an early date, and Dr. Mandlebaum thought he had come to a valuable conclusion.

DR. LARKIN said that Dr. Mandlebaum's statements did not apply to this case. This man had only a gangrene of his toe. His leg was amputated below the knee. He had a general endarteritis obliterans. While he did not doubt that Dr. Mandlebaum was perfectly correct as regards the eight cases to which he referred, these threw no light upon this particular case.





# INDEX

---

PROCEEDINGS

OF THE

NEW YORK PATHOLOGICAL  
SOCIETY

---

NEW SERIES, VOLUME VIII

1908



# I N D E X

	PAGE
<i>Acetone, Quantitative Determination of, in Urine—Hart....</i>	19
<i>Adenoma of Round Ligament—Wood.....</i>	148
<i>Ammonium Oxalate in Blood Culture Technique, Value of— Ryttenberg .....</i>	192
<i>Anemia, Pernicious, Colon Irrigations in Treatment of—Sat- terlee and Sabel .....</i>	69
<i>Arteries, Pulmonary, Arteriosclerosis of, Notes on—Zinsser..</i>	74
<i>Arteries, Radial Fibers in, (Duerck)—Oppenheimer.....</i>	81
<i>Arteriosclerosis of Pulmonary Arteries, Notes on—Zinsser...</i>	74
<i>Bile, Action of, on Pneumococcus, Streptococcus, and Strep- tococcus Mucosus—Libman and Rosenthal.....</i>	40
<i>Blood Cells, Red, Agglutinating Action of Ricin on, in Iso- tonic Sugar Solution—Field .....</i>	100
<i>Blood Culture Technique, Ammonium Oxalate in, Value of— Ryttenberg .....</i>	192
<i>Blood Cultures in Human Glanders—Crohn.....</i>	105
<i>Blood Cultures in Typhoid Fever—Epstein.....</i>	1
<i>Blood Vessels, Pathology of, in Gangrene of Lower Extremi- ties—Buerger .....</i>	49
<i>Bone Formation in the Kidney after Partial Extirpation— Pearce .....</i>	116
<i>Bone Sarcoma, Two Interesting Types of—Buerger.....</i>	111
<i>Buerger, L.—Pathology of the Vessels in Cases of Gangrene of the Lower Extremities due to so-called Endarteritis obliterans .....</i>	48
<i>Two Interesting Types of Bone Sarcoma.....</i>	111

	PAGE
<i>Carcinoma of Liver, Primary</i> —Wood.....	73
<i>Carlisle, R. J., and Martin, D. C.</i> —Case of Typhoid Fever associated with Cholelithiasis, Chronic Suppurative Cholecystitis, and Hepatic Abscesses.....	138
<i>Cecil, R. L.</i> —Study of the Pathological Anatomy of the Pancreas in Ninety Cases of Diabetes Mellitus...	202
<i>Celler, H. L.</i> —Specimens from Case of Gastro-Intestinal Pseudoleukemia .....	148
<i>Celler, H. L., and Mandelbaum, F. S.</i> —Lesions in a Case of Myasthenia Gravis .....	88
<i>Chloroform Poisoning, Delayed, Study of Metabolism and Pathology of</i> —Howland and Richards.....	161
<i>Colon Irrigations in Treatment of Pernicious Anemia</i> —Satterlee and Sabel .....	69
<i>Conjunctival Reaction (Ophthalgo-Tuberculin Test) Significance of</i> —Wolff-Eisner .....	124
<i>Crohn, B. B.</i> —Notes on Blood Cultures in Human Glanders..	105
 <i>Diabetes Mellitus, Pathological Anatomy of Pancreas in Ninety Cases of</i> —Cecil .....	202
 <i>Echinococcus Cyst of Liver with Rupture into the Ducts</i> —Libman and Crohn .....	45
<i>Endarteritis Obliterans, Pathology of Vessels in</i> —Buerger....	48
<i>Epstein, A. A.</i> —Blood Cultures in Typhoid Fever.....	1
<i>Epstein, A. A., and Ottenberg, R.</i> —Simple Method of Performing Serum Reactions .....	117
<i>Ewing, J.</i> —An Intrauterine Perithelioma .....	85
Myxoma and Diffuse Hyperplasia of a Full Term Placenta .....	84
 <i>Field, C. W.</i> —Agglutinating Action of Ricin on Erythrocytes in Isotonic Sugar Solution.....	100
 <i>Gall-bladder, Typhoid Bacilli in, Case of</i> —Zinsser.....	78
<i>Gangrene of Lower Extremities, Pathology of Vessels in Cases of</i> —Buerger .....	48
<i>Glanders, Human, Blood Cultures in</i> —Crohn.....	105
<i>Glands, Mesenteric, Tuberculosis of, Primary</i> —Hess.....	25

	PAGE
<i>Hart, T. S.</i> —A New Method for the Quantitative Determination of Acetone in Urine.....	19
<i>Hernia, Congenital False Diaphragmatic</i> —Martland.....	189
<i>Hess, A. F.</i> —Case of Tuberculosis in a Cat.....	104
Primary Tuberculosis of Mesenteric Glands: Report of Infections with Bacilli of the Human Type .....	25
<i>Hodgkin's Disease and Lymphosarcoma, Study of Cases of</i> —Longcope .....	153
<i>Howland, John, and Richards, A. N.</i> —An Experimental Study of the Metabolism and Pathology of Delayed Chloroform Poisoning .....	161
<i>Hypernephroma, Case of, with Metastases in Lungs</i> —Martland .....	34
<i>Jobling, J. W.</i> —Report on Mouse Tumors.....	101
<i>Kidney, Bone Formation in, after Partial Nephrectomy</i> —Pearce .....	116
<i>Kidney Tumors, Two Atypical</i> —Strauss.....	98
<i>Libman, E., and Crohn, B.</i> —Echinococcus Cyst of the Liver with Rupture into the Ducts; Cholangitis; Cholecystitis; Pneumococcemia .....	45
<i>Libman, E., and Rosenthal, J.</i> —Action of Bile on the Pneumococcus, Streptococcus, and Streptococcus mucosus... ..	40
<i>Liver, Carcinoma of, Primary</i> —Wood.....	73
<i>Liver, Echinococcus Cyst of</i> —Libman and Crohn.....	45
<i>Longcope, W. T.</i> —Study of Cases of Hodgkin's Disease and Lymphosarcoma .....	153
<i>Lymphosarcoma and Hodgkin's Disease, Study of Cases of</i> —Longcope .....	153
<i>Mandlebaum, F. S., and Celler, H. L.</i> —Lesions in a Case of Myasthenia Gravis .....	88
<i>Martin, D. C., and Carlisle, R. J.</i> —Case of Typhoid Fever Associated with Cholelithiasis, Chronic Suppurative Cholecystitis, and Hepatic Abscesses.....	138



<i>Martland, H. S.</i> —Case of Congenital False Diaphragmatic Hernia .....	189
Case of Hypernephroma with Extensive Metastases in Lungs .....	34
Case of Syphilitic Interstitial Splenitis with General Amyloid Disease .....	34
<i>Moschcowitz, E.</i> —Typhoid Fever with Mixed Infection.....	87
<i>Mouse Tumors, Report on</i> —Jobling.....	101
<i>Myasthenia Gravis, Lesions in a Case of</i> —Mandlebaum and Celler .....	88
<i>Myxoma and Diffuse Hyperplasia of Full Term Placenta</i> —Ewing .....	84
 <i>Oppenheimer, A.</i> —Radial Fibers in Arteries (Duerck).....	81
 <i>Pancreas, Pathological Anatomy of, in Ninety Cases of Diabetes Mellitus</i> —Cecil .....	202
<i>Pearce, R. M.</i> —Bone Formation in the Kidney after Partial Extirpation .....	116
<i>Perithelioma, Intrauterine</i> —Ewing .....	85
<i>Placenta, Myxoma and Diffuse Hyperplasia of</i> —Ewing.....	84
<i>Pneumococcus and Streptococcus, Action of Bile on</i> —Libman and Rosenthal .....	40
<i>Pseudoleukemia, Gastro-intestinal, Case of</i> —Celler.....	148
 <i>Radial Fibers in Arteries (Duerck)</i> —Oppenheimer.....	81
<i>Ricin, Agglutinating Action of, on Erythrocytes in Isotonic Sugar Solution</i> —Field .....	100
<i>Round Ligament, Adenoma of</i> —Wood.....	148
<i>Ryttenberg, Chas.</i> —On the Value of the Use of Ammonium Oxalate in Blood Culture Technique... ..	192
 <i>Sabel, S. O., and Satterlee, G. R.</i> —Colon Irrigations in Treatment of Pernicious Anemia .....	69
<i>Sarcoma, Bone, Two Interesting Types of</i> —Buerger.....	111
<i>Satterlee, G. R., and Sabel, O. S.</i> —Colon Irrigations in Treatment of Pernicious Anemia .....	69
<i>Serum Reactions, Simple Method of Performing</i> —Epstein and Ottenberg .....	117

<i>Splenitis, Syphilitic Interstitial, with General Amyloid Disease</i> —Martland .....	34
<i>Strauss, I.—Two Atypical Kidney Tumors</i> .....	98
<i>Streptococcus and Pneumococcus, Action of Bile on</i> —Libman and Rosenthal .....	40
<i>Tuberculin Test, Ophthalmic, Significance of</i> —Wolff-Eisner..	124
<i>Tuberculosis in a Cat</i> —Hess.....	104
<i>Tuberculosis of Mesenteric Glands, Primary</i> —Hess.....	25
<i>Tumors, Mouse, Report on</i> —Jobling.....	101
<i>Typhoid Bacilli in Gall-bladder</i> —Zinsser.....	78
<i>Typhoid Fever Associated with Cholelithiasis, Chronic Suppurative Cholecystitis, and Hepatic Abscesses</i> —Carlisle and Martin .....	138
<i>Typhoid Fever, Blood Cultures in</i> —Epstein.....	1
<i>Typhoid Fever with Mixed Infection</i> —Moschcowitz.....	87
<i>Wolff-Eisner, A.—Theoretical and Practical Considerations Concerning the Significance of the Con- junctival Reaction (Ophthalmic-Tuber- culin Test)</i> .....	124
<i>Wood, F. C.—Adenoma of Round Ligament</i> .....	148
Case of Primary Carcinoma of Liver.....	73
<i>Zinsser, H.—Case of Typhoid Bacilli in Gall-bladder</i> .....	78
Notes on Arteriosclerosis of Pulmonary Arteries.	74



# Proceedings

of the

## New York Pathological Society.

---

New Series, Vol. VIII.

FEBRUARY and MARCH, 1908

Nos. I and 2

---

### TABLE OF CONTENTS

EPSTEIN, Blood Cultures in Typhoid Fever.—HART, New Method for the Quantitative Determination of Acetone in the Urine.—HESS, Primary Tuberculosis of the Mesenteric Glands: Report of Infection with Bacilli of the Human Type.—MARTLAND, Case of Syphilitic Interstitial Splenitis with General Amyloid Disease; Case of Hypernephroma with Extensive Metastases in the Lungs.—LIBMAN AND ROSENTHAL, Action of Bile on Pneumococcus, Streptococcus, and Streptococcus Mucosus.—LIBMAN AND CROHN, Echinococcus Cyst of the Liver with Rupture into Ducts; Cholangitis; Cholecystitis; Pneumococcemia.—BUERGER, Pathology of the Vessels in Cases of Gangrene of the Lower Extremities due to so-called Endarteritis Obliterans.

---

DR. E. LIBMAN, *President.*

---

### BLOOD CULTURES IN TYPHOID FEVER.\*

BY ALBERT A. EPSTEIN, M.D.

(From the Pathological Laboratory of Mount Sinai Hospital.)

The principle established by Castellani and Schottnüller concerning the bacteriology of the blood in typhoid fever and the knowledge that we have in positive blood cultures a means of determining early and with certainty the presence of this disease,

\*Preliminary studies were presented before the New York Pathological Society in October, 1906.

have induced many investigators to search for methods of facilitating the work. The recent advances have, therefore, been mainly in the line of demonstrating the ease with which the work may be done. But as the literature indicates, the frequency of positive findings is not greater with the new than with some of the old methods.

Much of the difficulty hitherto experienced in cultivating the bacilli has been attributed to the bactericidal power of the blood. To overcome this hindrance, Castellani<sup>1</sup> used large quantities of bouillon and obtained positive results in 78 per cent. of the cases. Schottmüller<sup>2</sup>, however, used agar, the blood being present in the proportion of one to three of the medium. He was successful in finding the bacillus in 81 per cent. of the cases.\* Numerous other methods have been employed for cultivating the bacillus. Lemiere<sup>3</sup> was successful with cultures made from defibrinated blood. Eppenstein and Korte<sup>4</sup> grew the bacilli in oxalated blood. Müller and Graef<sup>5</sup> observed the growth of the bacilli in the fibrin network of clotted blood. Klodnitzky<sup>6</sup> succeeded in growing the bacilli from blood laked in ordinary sterile water. In twenty-five cultures made in our laboratory, we found multiplication of the bacilli in oxalated blood twenty-three times (without the addition of any nutrient material).

From these data it will at once be seen that the unfavorable influence of the blood upon the growth of the bacilli has been considerably overrated. We can not escape from the fact that with a variety of methods the results obtained by nearly all the investigators have been uniform. It seems that in working with one or another method many of the real conditions underlying the success or the failure of the work have been overlooked.

Thanks to the co-operation of the attending staff of the Hospital, I am able to report on one hundred and fifty-eight blood

\*If we adhere to the theory that the blood of a typhoid patient exerts marked inhibitory influence upon the development of the typhoid bacillus, Schottmüller's success in the work must be explained on the hypothesis of Eppenstein and Korte (4): that agar in solidifying destroys or diminishes the bactericidal properties of the blood.



cultures taken in one hundred and thirty-one cases of typhoid fever at different stages of the disease (this series includes two cases of paratyphoid, one of mixed infection with a streptococcus, and one case in which secondary infection by the pneumococcus occurred). The subject matter will be taken up in the following order:

1. A description of the technic of obtaining the blood, and of the media used.

2. The results, a comparison of the advantages of the various media, a note on the characteristic appearance of the colony of the typhoid bacillus in glucose agar, and a note on two cases of mixed infection.

3. The results in relapses.

4. The relationship of positive findings to the presence of the Widal reaction.

5. The relation of the bacteriemia to the stage, course, and severity of the disease.

6. The significance of negative cultures.

7. A note on the possible significance of the bacteriemia in relation to the prognosis.

8. Conclusions.

The method used in obtaining the blood is that introduced into the laboratory by Dr. Libman.<sup>7</sup> The blood is usually withdrawn from one of the veins in the bend of the elbow. In stout patients and in children, in whom these veins are often invisible or too small, a vein on the back of the hand or the dorsum of the foot has occasionally been used. It is wise to inspect these different parts first and see where one can best find a vein of sufficient size. After the constriction bandage has been applied above the part selected, and the field has been scrubbed with soap and water, it is rubbed with ether, alcohol, and, finally, a 1:500 solution of bichloride of mercury. Because a large number of media were used for each blood culture, it was necessary to withdraw

a moderately large quantity of blood, 10 c.c. or more. It will be shown later that although the use of so large an amount of blood increases the chances of obtaining a positive result, a smaller amount is usually sufficient. When the work was first taken up bouillon media were mainly used; later the series of eight media used as routine in the laboratory were employed. In the course of most of the recent work the following eleven media were used.

1. Plain nutrient bouillon (from meat infusion, 0.9 per cent. acid to phenolphthalein\*) in flasks containing 120 c.c.
2. Two per cent. glucose bouillon (titer and quantity like medium 1).
3. Plain nutrient agar (0.9 per cent. acid to phenolphthalein).
4. Plain nutrient agar to which  $\frac{1}{4}$  to  $\frac{1}{3}$  volume of ascitic serum had been added.
5. Two per cent. glucose agar (titer same as that of the plain agar).
6. Two per cent. glucose agar with  $\frac{1}{4}$  to  $\frac{1}{3}$  volume of ascitic serum.
7. Plain agar (neutral in reaction to phenolphthalein).
8. Five per cent. glycerin agar (0.9 per cent. acid).
9. Ten c.c. of Conradi's bile medium.
10. Five c.c. of Kayser's bile medium.
11. Ten c.c. of a 0.2 per cent. solution of ammonium oxalate.

The work was more or less developmental in character, and was carried on without any preconceived notions concerning the possible merits of one or another medium. (The eight media referred to above as belonging to our routine series were numbers 1 to 8 on the list.) The latest studies were made with media 1, 2, 5, 9, 10 and 11. The oxalated solution was used for two reasons: first, to test the growth of bacilli in oxalated blood

\*The titer of 0.9 per cent. acid was chosen because it was found to give a better growth of typhoid bacilli than more acid media.

without the addition of any nutrient material; and, second, to test the efficiency of this solution as an intermediate measure in blood culture work between the bedside and the laboratory.<sup>8</sup> In the use of the bile media, the directions given by Conradi<sup>9</sup> and Kayser<sup>10</sup> were closely followed. In each series, after the blood was withdrawn it was rapidly distributed into the media and incubated at 37.5° C.

The cultures were observed from three to seven days, and careful records were made both as to the time of appearance and the features of the growths. The following summaries give the results obtained with the different media.

## SUMMARY No. I.

Medium	Number of Cultures	Amount of Blood	Posi- tive Results	Nega- tive Results	Result in Percent- age	Time in Hours
1. Plain bouillon.....	81	2 c.c.	61	20	75%	48
2. 2% glucose bouillon	86	2 c.c.	70	16	81.4%	38
3. Plain agar .....	31	2 c.c.	12	19	38.7%	50
4. Plain agar and se- rum .....	26	1.5 c.c.	8	18	31%	68
5. 2% glucose agar ....	83	2 c.c.	67	16	80%	31
6. 2% glucose agar and serum .....	20	1.5 c.c.	8	12	40%	58
7. Neutral plain agar	16	1.5 c.c.	1	15	6.66%	—
8. 5% glycerin agar....	32	2 c.c.	12	20	37.5%	68
9. Conradi (10 c.c.) ...	28	1.5 c.c.	16	12	57.5%	26
10. Kayser (5 c.c.).....	29	2 c.c.	17	12	58.375%	31
11. Ammonium oxalate solution (10 c.c.) ...	25	3.5 c.c.	23	2	92%	29

## SUMMARY No. II.

## The Two Bouillons Compared.

Both bouillons used simultaneously in 80 positive cultures.

Both bouillons positive in 51 cultures—63.7%.

Both bouillons negative in 8 cultures—10%.

Plain bouillon positive, 2% glucose bouillon negative, in 7 cultures—8.7%.

Plain bouillon negative, 2% glucose bouillon positive, in 14 cultures—17.5%.

So that in all, plain bouillon was positive in 58 out of 80 cultures—72.5% ; and 2% glucose bouillon was positive in 65 of the cultures—81.25%. Total positive results for both bouillons—90%.

The average total amount of blood used for the bouillon media was 4 c.c. per culture.

### SUMMARY No. III.

#### Agar Media Compared.

A. Plain agar, 2% glucose agar, used together in 26 cultures.

Both positive in 10 cultures—38.4%.

Both negative in 3 cultures—11.5%.

Glucose agar positive alone in 13 cultures—50%.

Plain agar positive alone in 0 cultures—0%.

B. 5% glycerin agar, 2% glucose agar, used together in 31 cultures.

Both positive in 10 cultures—30.1%.

Glycerin agar positive, glucose agar negative, in 2 cultures—6.2%.

Glycerin agar negative, glucose agar positive, in 14 cultures—45.16%.

Of the total number of 31 cultures, 2% glucose agar was positive in 24 cultures—77.4% ; whereas glycerin agar was positive in 12 cultures—38.4%.

### SUMMARY No. IV.

#### Bile Media Compared.

Both media used in 27 cultures.

Both media positive in 11 cultures—41.8%.

Both media negative in 6 cultures—22.2%.

Conradi medium positive, Kayser medium negative, in 4 cultures—14.8%.

Kayser medium positive, Conradi medium negative, in 6 cultures—22.2%.

In the 27 cultures in which both bile media were used, the total positive results obtained were 21 cultures—77.78%.

The average total amount of blood used for the bile media was 3.5 c.c. per culture.

### SUMMARY No. V.

#### Ammonium Oxalate Solution Compared with Other Media.

Ammonium oxalate solution used in 25 cultures; positive in 23.

*A.* Ammonium oxalate solution, plain bouillon, used together in 19 cultures.

Growth appeared in the oxalated blood in 17 cultures, and in plain bouillon in 13 cultures.

*B.* Ammonium oxalate solution, 2% glucose bouillon, used together in 20 cultures.

Growth in oxalated blood in 18 cultures, and in glucose bouillon in 17 cultures.

*C.* Ammonium oxalate solution, 2% glucose agar, used together in 23 cultures.

Growth in oxalated blood in 21 cultures, and in glucose agar in 20 cultures.

*D.* Ammonium oxalate solution, Conradi medium, Kayser medium, used together in 13 cultures.

Growth in oxalated blood in 11 cultures, in Conradi's medium in 8 cultures, and in Kayser's medium in 7 cultures.

The average amount of blood used in this medium was 3.5 c.c.

In studying these results we can readily see which media appear to be best suited for the work. We find that the media



can be arranged in two groups, one of which is distinctly favorable to the growth of the bacilli, and another of which is unfavorable. It is evident, of course, that the word "unfavorable" must be used cautiously because in any one blood culture the organisms may be few in number and therefore may appear on some of the media and not on others. In such instances it is greatly a matter of chance which medium gives positive results. The bacterial invasion of the blood in typhoid fever appears to be more uneven than it is in infections by other bacteria, for even in some cases where the bacteria are comparatively numerous, we find that the given amount of blood divided equally into like portions of the same medium gives an unequal number of colonies in each portion. This difference is at times very striking. Müller and Graef in their cultures from clotted blood had the same experience. I am not able to say what the cause of the uneven distribution is; possibly clumping of the organisms plays some part. I have at times found that fully developed colonies of typhoid bacilli (of the type to be later described) would appear on 2% glucose agar within the first sixteen hours of incubation, and then thirty-six to forty-eight hours might elapse before any more colonies appeared on the same plate. We must assume from this fact that as a result of a conglomeration or actual clumping, the respective colonies arise from different numbers of bacilli.

In this connection it may be stated that in the entire series of one hundred and fifty-eight cultures, I have at no time seen so large a number of bacteria in the blood as that observed by Schottmüller and Schüffner.<sup>2</sup> Whether this difference is due to the difference in the type of cases studied or not, we can not determine; possibly differences in technic may account for the discrepancy.

From the study of the variations which occur in the number and growth on the different media and different portions of the same media, I am inclined to the belief that up to a certain degree the media exert but little influence on the result of the culture. The bacilli will grow on any medium provided such a medium is not actually antagonistic. It appears that bacilli fail to grow

well in neutral media and in media the titer of which is above 0.9 per cent. acid. The experiments of Müller and Graef with clotted blood, as well as those of Eppenstein and Korte with oxalated blood, and those of Meyerstein with bile salts, led to the belief that the fluidity of the blood was essential to the development of the bacilli. The later work of Müller and Graef showed that the fluid state of the blood for growth is not necessary, as they observed the growth in the fibrin network of clotted blood.

It is likely that a number of bacilli which reach a culture medium are impaired in their vitality in consequence of the detrimental influences to which they are exposed in the body; so that the blood withdrawn for the culture may contain bacilli few of which, if any, are viable. But the claim so frequently made that the failure of the bacteria to grow is wholly due to the continuation of the bactericidal action of the blood (in vitro) is not supported by experience. The work of Eppenstein and Korte bears evidence to the contrary. They conclude from their experiments that the bacillus develops an immunity against the bactericidal action of the blood of the host. This view gains support from the fact that the bacteria multiply in defibrinated, oxalated, laked and clotted blood without the addition of any nutrient medium.

What has been said of the cultures on ordinary media applies also to the bile media of Conradi and Kayser. The results with these methods show no advantages over the ordinary methods. My own results indicate a distinct disadvantage. I found no evidence that bile uniformly augments the growth of the bacilli. The experiments which Meyerstein<sup>12</sup> recently performed proved that the bile salts do not possess any "anreicherung" influence upon the growth of the typhoid bacilli. His observations, as well as those of Nicolle and Adil-Bey<sup>13</sup> and those of Levy<sup>14</sup>, show moreover that these salts exert a detrimental influence upon the growth of other organisms. In conditions therefore, which simulate typhoid fever and in which other organisms than the typhoid bacillus may be present in the blood, our knowledge of the inhibitory influence of bile on certain bacteria (for instance, the pneumococcus) makes it evident that a negative result might

be obtained whereas the use of the ordinary media might have resulted in a positive finding, and, as we have seen, the ordinary media will also not interfere with the development of the typhoid bacillus.

I wish to draw particular attention to the use of 2 per cent. glucose agar.<sup>7</sup> This medium not only permits good growth of the typhoid bacillus and other organisms,\* but the colonies of the typhoid bacillus develop in it in a characteristic way. The features of the colonies on the medium are as follows: They usually appear in the first twenty-four to thirty-six hours of incubation, and are pin-point in size with a disproportionately wide area of green coloration around them. This areola is well defined at the circumference and may be limited by a ring of darkened blood. The colonies show little tendency to increase in size for the first two or three days, whereas the surrounding green areola widens very rapidly. This description applies only to colonies of typhoid bacilli in the depths of the medium. The surface colonies also develop a green color, but they are much larger than the deep colonies and present nothing that may be considered characteristic.

The development of a green coloration about the colonies in the glucose blood medium is a feature that is not restricted to the typhoid bacillus itself; other bacteria may give rise to the same phenomenon. Ruediger<sup>15</sup> studied the question of the production of this pigmentation and found that the pneumococcus, the streptococcus, the *Staphylococcus aureus*, and the typhoid bacillus produce it; whereas *B. coli* does not, producing instead a rapid and diffuse hemolysis. From our experience, however, the only colonies that need to be considered from a differential standpoint are those of the *Staphylococcus aureus*, the *B. coli*, and the paracolon group. The *Staphylococcus aureus* grows usually in much larger and more disc-like colonies; and in addition to the green color which it produces, there develops within twenty-four to thirty-six

\*Although this medium is better than the bile media for routine work, in connection with other bacteria than typhoid bacillus, it is sometimes not so good as agar unless serum be added.

hours, a clear area (complete hemolysis) immediately around the colonies between them and the area of green coloration. This hemolytic ring may be very narrow and in the early stages of incubation may be entirely absent.

In one case of general infection by the colon bacillus, which we had the opportunity of studying, the colonies in the glucose medium developed to a much larger size within the given period than do colonies of typhoid bacillus. They showed, moreover, a greater tendency to break through and spread out upon the surface of the medium, and produced gas. Gas bubbles were also produced by the paracolon bacillus; but the colonies otherwise resembled very closely those of typhoid bacillus.

When, therefore, we find that stained smears from the colonies of the type described as characteristic for the typhoid bacillus show the presence of a Gram negative bacillus, we can safely place the organism in the typhoid-colon group.\* Moreover, when colonies are present on the media, which do not correspond to the type described, the presence of the typhoid bacillus may be excluded. The character of the colony which the typhoid bacillus produces on 2 per cent. glucose blood agar affords us, then, a great help in identifying the organism early. Most of our positive results on the glucose agar were obtained within twenty-four hours after taking the culture. In some instances the typical typhoid colony developed within sixteen hours. Delay in development of the colonies may at times be accounted for by errors in the titer of the medium.

Of the one hundred and fifty-four cultures taken promiscuously, some for diagnosis and others for research, one hundred and ten gave growths of typhoid bacillus and two of paracolon (so-called paratyphoid) bacilli. In one case of typhoid fever complicated by pneumonia and otitis media, a streptococcus was obtained from the blood. The typhoid bacillus was no longer present (the Widal reaction was positive). In another

\*All the bacilli isolated in our cases were, of course, further identified by the study of their cultural features and by the presence of agglutination with immune typhoid serum.

case, studied through the kindness of Dr. Eli Moschcowitz, both the typhoid bacillus and a streptococcus were found in the same culture. The results obtained with 2 per cent. glucose bouillon, 2 per cent. glucose agar, and ammonium oxalate solution were the most encouraging; so that our experience leads us to suggest the use of these three media for diagnostic work.

As for the quantity of blood, it may be said that 2 c.c. are sufficient to give positive results in 80 to 85 per cent. of positive cases; but where a larger amount of blood can be withdrawn without inconvenience, it is desirable to obtain it, especially in the later weeks of the disease when the organisms are apt to be very few in number. It is necessary to draw attention to the fact that while the total percentage of our positive results is about the same as that given by other authors, most of our cases were studied during the third and fourth week, and as the results are generally considered to be better in the first and second week, the methods which we have decided to adopt for routine work seem to promise better results than the methods generally used.

#### SUMMARY No. VI.

Week of Disease	Number of Cultures	Cultures positive	Widal positive
1	8	7—88.5%	2—28.5%
2	44	39—88.6%	28—63.5%
3	42	25—60%	36—86%
4	15	8—53.33%	12—80%
5	1	5—71.5%	5—71.5%
6	3	1—33.33%	3—100%
7	3	1—33.33%	2—66.66%
Totals . . . . .	122	86—71%	88—72.8%



## SUMMARY No. VII.

## RELAPSES.

Intercurrent relapses, 5—all positive		
Day of relapse	Number of cases	Result of culture positive
2	5	3
3	5	4
4	2	1
5	4	4
6	2	2
7	2	1
11	1	1
12	1	0
14	1	0

The last two summaries permit us to draw certain deductions concerning the efficiency of the blood culture as a diagnostic means in that stage of the disease when other means are unavailing. They also draw our attention to the investigation of the relationship of the bacteriemia to the course of the disease. As shown in Summary No. VI, and as already mentioned above, the results obtained agree in general with those of other investigators. The relationship of the positive blood culture and the positive Widal reaction has been studied by a number of authors. The statistics of Coleman and Buxton<sup>16</sup> show that many of the positive cultures antedate the presence of the Widal reaction. Ghaetghens' studies showed that of 917 Widal tests made, in the first week of the disease 25 per cent. were negative, in the second 10 per cent., and in the third 4.7 per cent. He also found that in 140 cases in which the Widal reaction remained negative, 34 were diagnosed by positive blood cultures, an experience previously shared by a number of other observers. Our own results confirm the previous observations.

The lack of relationship between the result of the culture and the type and severity of the disease has also been noted by nearly

all the writers who have reported on large series of cases. Though some fever is usually present at the time when the blood culture is positive, there is no direct dependence of the result upon the height of the temperature. A positive result may be obtained with the temperature at  $100^{\circ}$  F. as frequently as at  $105^{\circ}$  or  $106^{\circ}$ , provided such a temperature occurs in the course of the active stage of the disease. A number of our cases yielded positive results shortly before defervescence, that is, within one, two, or three days; but in no case was a positive result obtained after defervescence was established. Conradi's results in afebrile cases of the disease are certainly exceptional. Coleman and Buxton state that in cases with a long duration, the bacillus is in the blood as long as the temperature persists. My own results support this view in part only. We must distinguish in prolonged cases between those in which the prolongation is due to the disease itself, and those in which prolongation is due to some complication (such as phlebitis or bronchopneumonia, etc.). In the former group of prolonged cases, positive results may be expected. The cases with intercurrent relapses may be regarded in the same group as the last mentioned. The five cultures of our series which were taken in such cases were all positive (see Summary No. VII).

We have had the opportunity of studying twenty-three relapses, sixteen of these gave positive results, approximately 70 per cent., a figure which is nearly the same as that given by a study of the primary attacks. Our experience with negative cultures during the afebrile period warrants the conclusion that in the relapse we are dealing, not with the continuation of the original bacteriemia, but with a new bacteriemia. In the intercurrent relapse it is possible that the bacteriemia is continuous with the original bacteriemia. In four of the sixteen cases of relapse with positive results, negative results were obtained in the primary attack. An analysis of the results obtained on different days of relapse shows (although the series is too small as yet to be conclusive) that the results are better when the fever nears the fastigium than they are in the earlier days. In one case we had the

opportunity of making cultures on the third, seventh, and eleventh days of a relapse. The first two cultures were negative and the third positive. This observation also confirms the view expressed by Schottmüller, that in the true relapse there is a new invasion of the blood.

From a consideration of the results obtained by most investigators it appears to be certain that the bacteremia is concerned in the production of at least some of the clinical aspects of the disease. As Coleman and Buxton state, the number of positive cultures is such that one must conclude that the typhoid bacillus is present in the blood in every case of typhoid fever at some time or other. My own studies with the different media indicate that negative results in the early stages of the disease are accidental. These observations are important, not only from the standpoint of etiological and pathological studies, but also from the standpoint of diagnosis, for they show that a continued fever (and this conclusion was drawn by Schottmüller, and later by Libman<sup>18</sup>) which lasts for several days after the cultures have shown the blood to be free from typhoid bacilli is in all probability not a case of typhoid fever.

To sum up: all the results hitherto obtained show that in typhoid fever there is a bacteriemia which becomes progressively less marked as the disease goes on. Whether the cases which extend beyond the third, fourth and fifth weeks, and in which positive results are obtained, are due to repeated invasions of the blood current or not, is a question which can not, at present, be decided. From the present state of our knowledge it is difficult to formulate a definite view of the significance of the bacteriemia in typhoid fever. The case recently published by Conradi<sup>19</sup> in which bacilli were present in the blood before the onset of the fever, and the case described by Widal in which a positive blood culture was obtained on the second day of the disease, would appear to lend strength to the view of Schottmüller concerning the close relation of the bacillemia to the fever. Certain facts presented by our own studies make us hesitant concerning the occurrence of bacillemia from the very inception of the disease.

for in one case the culture taken on the fifth day was negative, and another culture taken a few days later was positive. In the second case, two cultures taken during a relapse were negative, and the third positive. We are in need of some studies of cases in which the blood cultures were made on the first or second day of the disease (or the relapse).

Our studies do not warrant us in drawing any conclusions concerning the relation of the number of bacilli present to the prognosis of a given case. Schottmüller and Schüffner are of the belief that there is a relationship. Further studies in this direction are also desirable. It is not at all unlikely that the study of the biological differences of the organisms from the blood of different patients will throw some light concerning both prognosis and therapy.

Our studies permit us to draw the following conclusions:

1. The bactericidal influence of the blood in typhoid fever in relation to the obtaining of positive results in the blood cultures has been overestimated. Great dilutions of the blood are not essential; a number of media will give good results.

2. The best results in our experience were obtained with the use of 2 per cent. glucose bouillon, 2 per cent. glucose agar, and ammonium oxalate solution.

3. On 2 per cent. glucose agar the typhoid bacillus grows in such a characteristic way that the presence of a certain type of colony on it is quite disagnostic and the absence of such a colony points very strongly against the presence of the typhoid bacillus.

4. The bile media were not found to be as reliable as the media mentioned above.

5. The results presented are in agreement with those obtained by others. The total positive results obtained by us are in agreement with the results obtained by others notwithstanding the fact that more of our cases were studied later in the course of the disease.

6. Although the maximum results are obtained in the first and second week there is not sufficient proof as yet that the bacilli are present in the blood from the very inception of the fever.

7. Protracted cases yield positive results if the continuation of the fever is not due to complications (or starvation).

8. A continued fever lasting several days after the blood has been shown to be free from typhoid bacilli will nearly always prove not to be a case of fever.

9. The results in relapses are the same as those in the primary attacks. The bacillemia in the relapses is due to a new invasion.

10. We can not draw any definite conclusions, as yet, concerning the value of the blood cultures in determining the prognosis.

It is with a deep sense of gratitude that I wish to acknowledge my indebtedness to Dr. E. Libman for his advice and constant guidance in this work. To Drs. Hertz, Ryttenburg and Fried, I wish to express my thanks for their kind assistance.

#### References.

- 1 CASTELLANI. *Settimana Medica*, 1899.
- 2 SCHOTTMÜLLER. *Münch. med. Woch.*, 1902, No. 38.
- 3 LEMIERE. *Ibid.*, 1906, No. 32.
- 4 EPPENSTEIN AND KORTE. *Ibid.*, 1906, No. 24.
- 5 MÜLLER AND GRAEF. *Centralbl. f. Bakt.*, xliii, 1907.
- 6 KLODNITZKY. *Russki Vrach.*, vol. VI, Nos. 27, 28, 29.
- 7 LIBMAN. *Johns Hopkins Hosp. Bull.*, 1906, July.
- 8 EPSTEIN. *Amer. Jour. Med. Sciences*, 1907, Sept.
- 9 CONRADI. *Münch. med. Woch.*, 1906, No. 34.
- 10 KAYSER. *Ibid.*, 1906, No. 17.
- 11 SCHÜFFNER. *Ibid.*, 1907, No. 35.
- 12 MEYERSTEIN. *Centralbl. f. Bakt.*, xliv, 1907.
- 13 NICOLLE ET ADIL-BEY. *Ann. de l'institut Pasteur*, 1907, No. I.
- 14 LEVY. *Virchows Arch.*, 1907, Feb.
- 15 RUEDIGER. *Jour. Infectious Dis.*, 1907, Sept.
- 16 COLEMAN AND BUXTON. *Amer. Jour. Med. Sciences*, 1907, June.
- 17 GHAETGHENS. *Arb. a. d. Kais. Gesundheitsamte*, 1907, H. 1
- 18 LIBMAN. *Trans. N. Y. Academy of Medicine*, 1907, Mar. 7.
- 19 CONRADI. *Münch. med. Woch.*, 1907, No. 41.



*Discussion.*

DR. THOMAS FLOURNOY asked as to the details of the dilution of the blood by the media.

DR. EPSTEIN said that he had used 100 to 120 c.c. of plain bouillon and 2 per cent. glucose bouillon, and to that quantity he had added about 2 c.c. of blood.

DR. CHARLES NORRIS said that he thought Dr. Epstein's paper very admirable and sane. He was pleased that Dr. Epstein had found that the bile salt method was not so good as it was at first considered. He had always thought it a comparatively easy thing to get growth on any bouillon in a few days. An important point was never to throw away a blood flask before five or six days. Not infrequently clouding of the broth did not appear until the third or fourth day.

DR. E. LIBMAN wished to emphasize two or three points. In the first place, there was the necessity for studying a large number of cases carefully in order to see whether the point made by Dr. Epstein would be confirmed; that is, that if the temperature remain nearly constant for several days after a negative blood culture, typhoid fever could be excluded. Several cases recently seen tended to confirm this statement. There was also a necessity for full studies on the bacteriemia in the first few days of the disease. Upon the results of such studies would depend greatly our conception of the etiology of typhoid fever. Personally, he thought one could not yet be sure of the conclusion that the bacilleamia is the cause of the lesions. It was still undecided whether the lesions in the intestine caused the bacilleamia or the bacilleamia caused the intestinal lesions.

---

## A NEW METHOD FOR THE QUANTITATIVE DETERMINATION OF ACETONE IN THE URINE.

T. STUART HART, M.D.

(From the Laboratory of Dr. E. G. Janeway.)

Although a number of methods have been devised for the quantitative estimation of acetone in the urine, at the present time the method of Messinger,<sup>1</sup> as modified by Huppert,<sup>2</sup> is the one most frequently employed, and is usually regarded as the most accurate one at our command.<sup>3</sup>

A recent paper by Folin<sup>4</sup> offers the first satisfactory method for separately determining the acetone and diacetic acid of the urine. By this method, acetone and diacetic acid are estimated by the Messinger-Huppert method; acetone is separately estimated by drawing it into a suitable absorbing solution by means of a current of air. From these data the diacetic acid may be calculated by subtracting the amount of acetone obtained by means of the air current, from the acetone determined by the Messinger-Huppert method. Folin has shown that under the conditions of his method practically all of the acetone in 20 c.c. of urine is by a continuous current of air, in twenty-five minutes, transferred to the absorbing cylinder, and may there be rapidly estimated by titration. In a preceding paper, I have shown that my experiments following those of Folin corroborate the correctness of his statements.

While working with Folin's method, the thought occurred to me that if we could convert diacetic acid into acetone, both could be transferred by a current of air to the absorbing bottle, and we could thus obtain a short method for the estimation of acetone and diacetic acid in the terms of acetone. The conversion of diacetic acid into acetone and carbonic acid is readily accomplished by heating to the boiling point. The determination is conducted in the following manner:

The apparatus used is a slight modification of one devised by Folin for the estimation of ammonia.<sup>5</sup>

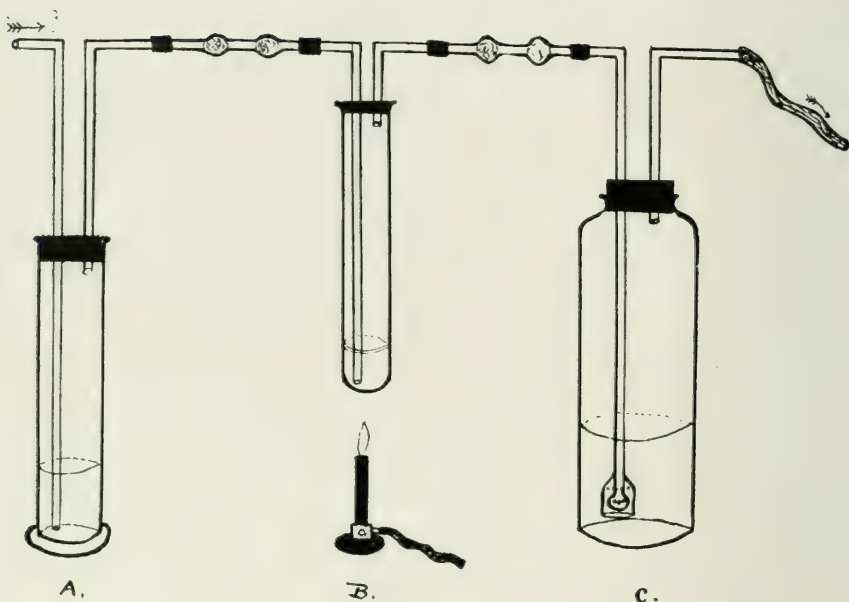


Diagram.

A is an aerometer cylinder.

B is a large test tube, two inches in diameter, raised so that it can be easily heated.

C is a wide-mouthed bottle fitted with a Folin tube.<sup>6</sup> The connections between the cylinders are made with bulk tubes containing cotton.

A contains alkaline hypiodite to absorb any acetone which may be present in the laboratory air.

B contains 20 c.c. of the urine to be examined, 10 drops of a 10 per cent. solution of phosphoric acid, 10 grams of sodium chloride, and a little petroleum.

C contains 200 c.c. of distilled water, an excess of decinormal solution of iodine (carefully measured), and an excess of 40 per cent. solution of sodium hydrate.

The apparatus is then connected with a Chapman pump and a steady current of air is drawn through at a moderate rate for twenty-five minutes. During this period, a lamp is placed under the tube containing the urine and the contents brought just to a

boil; this is done twice, allowing an intermediate period of about five minutes.

By the application of heat the diacetic acid is converted into acetone, and at the end of twenty-five minutes will have been drawn into the absorbing bottle and have been converted into iodoform.

The contents of the absorbing bottle (C) are now acidulated with strong hydrochloric acid, when if iodine be present in excess a brown color will develop. This is now titrated with a decinormal solution of sodium thiosulphate, using starch as an indicator as in the Messinger-Huppert method. The amount of iodine used in the formation of iodoform is calculated by subtracting the quantity of thiosulphate solution used from the quantity of decinormal iodine solution placed in the absorbing bottle. One c.c. of the iodine solution is equivalent to 0.976 mgms. of acetone.

The following are a few results obtained in diabetic urines, with comparative findings by the Messinger-Huppert method:

No.	Date 1908	Messinger- Huppert Method.	Author's Method.	Difference	Difference
		Grams per liter	Grams per liter	Grams per liter.	Per cent.
1	Jan. 9	1.430	1.440	+0.010	+0.7
2	" 11	0.766	0.703	-0.063	-8.2
3	" 13	0.878	0.888	+0.010	+1.1
4	" 14	1.425	1.469	+0.044	+3.1
5	" 14	0.629	0.570	-0.059	-9.3

In experiments 1, 2 and 5, after twenty-five minutes of air current and heat by the described method, a trace of acetone was found in the tube containing the urine; at times the air current was probably a little too slow in these determinations.

In three of the above determinations, the estimation was a little high, and in two the estimation was considerably too low as compared with the Messinger-Huppert method. The low determinations may be explained by the fact that the air current

was too slow, as in each a trace of acetone could be detected in the original urine after the air current had passed for twenty-five minutes. The investigations of Schwartz<sup>7</sup> show that he was able to recover 96 to 97 per cent. of the acetone of the urine by the Messinger-Huppert method.

This method may be used in conjunction with Folin's method to estimate the relative amounts of acetone and diacetic acid in the urine. The apparatus and solutions are prepared as described above and an air current drawn through the urine for twenty-five minutes without the application of heat. By this means, as suggested by Folin, all the acetone is drawn into the absorbing bottle and may be estimated by titration. A fresh alkaline hypiodite solution is then placed in the absorbing bottle; heat is applied to the urine tube to convert the diacetic acid into acetone; and this is drawn off by an air current for twenty-five minutes as above described, and is in turn estimated by titration.

The following table shows a few results obtained by this method, and a comparison of these with the results obtained by the Messinger-Huppert method.

Aceton in grams per liter.							
No.	Date 1908	I Air Current 25 mins.	II Following I Air Current and heat 25 mins.	III Total I and II	IV Messinger- Huppert Method	V Differ. III and IV	Differ. Per cent
1	Jan. 27	0.142	0.390	0.532	0.561	-0.029	-5.4
2	" 28	0.234	0.781	1.015	1.056	-0.041	-3.4
3	" 30	0.098	0.561	0.659	0.675	-0.016	-2.4
4	Feb. 4	0.132	0.473	1.605	0.625	-0.020	-3.2

Note:—No. 1. Air current was very slow; at the end of the determination acetone could be detected in the urine.

Nos. 2 and 3. No acetone could be detected at the end of the determinations.

No. 4. A trace of acetone detected after determination.



The method as proposed affords values approximating very closely to those of the Messinger-Huppert procedure, while the time required for a determination is only half an hour as against two to two and one-half hours demanded by the Messinger-Huppert process.

Note:—To obtain a rough idea of the amount of decinormal iodine solution needed in the absorbing bottle, mix in a test tube 10 c. c. of the urine to be examined and 1 c. c. of a 100 per cent. solution of ferric chloride. Allow this to stand for two minutes and compare the color thus developed with the color of 100 per cent. ferric chloride solution in a test tube of equal size. If the color of the two test tubes be approximately of the same depth, 10 c. c. decinormal iodine solution will be sufficient to combine with the acetone set free from 20 c. c. of urine. If the color of the urine mixture be darker than that of the ferric chloride solution, dilute the urine mixture with distilled water until its color approximates in depth the color of the ferric chloride solution. The amount of decinormal iodine needed can then be roughly estimated as follows:

Urine       $\text{Fe}_2\text{Cl}_6$   
(100% sol.)

10 c.c. + 1 c.c. . . . . = needed 10 c.c. decinormal iodine sol.

$\text{H}_2\text{O}$

10 c.c. + 1 c.c. + 10 c.c. = needed 20 c.c. decinormal iodine sol.

10 c.c. + 1 c.c. + 20 c.c. = needed 35 c.c. decinormal iodine sol.

10 c.c. + 1 c.c. + 30 c.c. = needed 50 c.c. decinormal iodine sol.

### References.

- 1 MESSINGER. *Ber. d. chem. Ges.*, 21, 1888.
- 2 HUPPERT. *Anal. des Harns*, 1898.
- 3 WALDVOGEL. *Die Acetonkörper*, 1903, p. 14.
- 4 FOLIN. *Jour. of Biol. Chem.*, III, 1907, p. 177.
- 5 FOLIN. *Zeit. f. physiol. Chemie*, XXXVII, 1902, p. 161.
- 6 FOLIN. *Jour. of Biol. Chem.*, III, 1907, p. 182.
- 7 SCHWARZ. *Arch. f. exp. Path. u. Pharm.*, XL, 1898.

*Discussion.*

DR. A. MAYER said that he thought this was the best method for the determination of acetone and diacetic acid that he knew of. Shortly before the publication of Folin's paper, Embden, of Frankfort, studied this question and read the results of his studies before the Kongress für innere Medizin of 1907. His method somewhat resembled this, but differed in that Embden distils the acetone from the urine, using a temperature of only  $35^{\circ}$  C. He found that was sufficient to distil over the entire acetone in the urine. He then raised the urine to boiling point, converting the diacetic acid into acetone, and in that way got two quantities, the first representing the free acetone in the urine, and the second, the acetone derived from diacetic acid. Dr. Mayer thought Dr. Hart's method superior to this, because a temperature of  $35^{\circ}$  C. was exceedingly difficult to regulate; and a temperature running higher would certainly convert the diacetic acid into acetone. The simplicity of the method was greatly in its favor. Whether the ammonia which is contained in all these urines might have some influence in the determination of the acetone, was a question which should be studied. All of the diabetic urines containing large quantities of acetone and diacetic acid also contain large quantities of ammonia, and ammonia may be drawn over in the same way as the acetone. It was a question whether the ammonia had any influence on the iodine solution.

DR. HART regretted that he was not familiar with Embden's work on this subject. Other attempts had been made on these lines, which had not been successful in some details. Strauss attempted something in the same line, but apparently used too large quantities of urine, since it was necessary for him to continue the procedure for twenty hours. As regarded the ammonia, Dr. Hart thought that the phosphoric acid added to the urine would hold back the ammonia by neutralizing it; so that the error was not very considerable.

---

PRIMARY TUBERCULOSIS OF THE MESENTERIC  
GLANDS: REPORT OF INFECTIONS WITH  
BACILLI OF THE HUMAN TYPE.

BY ALFRED F. HESS, M.D.

Before reporting the cases which form the subject of this paper, it may be both profitable and interesting to bring together all other instances in which tubercle bacilli have been found, cultivated, and differentiated in mesenteric glands, in order to see whether we are justified in drawing any general conclusions. I shall not consider the question of the frequency with which primary mesenteric tuberculosis is encountered. This is a subject concerning which inexplicable differences of opinion still exist, as is indicated by a comparison of the English statistics, which show a primary lesion of the intestine and its glands 290 times among 1,560 autopsies of children, that is to say, in 18.6 per cent., with those of 369 cases of tuberculosis coming to autopsy in New York and its environs, among which only five were of intestinal origin, a little more than 1.3 per cent.<sup>1</sup>

Leaving this question open, let us turn to those cases in which the type of infecting organism has been isolated and studied. On reviewing the literature I have been able to find seventy-one instances where this procedure has been followed. This list may not include all, but it certainly comprises the great majority of cases, and is sufficient for a trustworthy analysis.

Eighteen cultures were studied by the British Tuberculosis Commission, twenty-seven by the German Commission, and twenty-six by other investigators. A cursory review of these cases, best seen when they are arranged in tabular form (Table I) brings to light the fact that the majority are instances of infection with the bovine type of bacillus; in fact, forty-four of the seventy-one, or 62 per cent., are of this nature. These figures are not conclusive in the decision of the question as to the relative importance of bovine and human infection in general, for they consider only one group of cases, and, as I have said elsewhere,<sup>2</sup> only a consideration of a large number of unselected cases of

TABLE I.

A Summary of Reported Cases of Primary Mesenteric Tuberculosis.

	Human		Bovine	
	Children	Adults	Children	Adults
British Tuberculosis Commission .....	8	....	10	....
German Tuberculosis Commission* ....	7	5	15	....
SMITH ..... <i>Trans. Ass'n American Physicians.</i>	1	....	1	....
SMITH ..... <i>Amer. Jour. Med. Sciences, 1904</i>	1	2	....	....
SMITH AND BROWN..... <i>Jour. of Med. Research, Sept. 1907</i>	....	1	1	....
RAVENEL ..... <i>Univ. Penn. Med. Bull., 1902</i>	...	....	1	....
DESCHWEINITZ, DORSET AND SCHROEDER <i>Bureau Animal Ind., Bull. 52, ii, '05</i>	....	....	2	....
FIBIGER AND JENSEN <sup>o</sup> ..... <i>Berl. klin. Woch., 1902, 1904, 1907</i>	1	1	5	....
DAMANN AND MÜSSEMEIER ..... <i>Untersuch. d. Tb. der Mens. u. Tiere,</i> <i>1905</i>	....	....	....	1
HOELZINGER ... <i>Inaug. Diss. Giessen, 1907</i> .....	....	....	....	1
L. RABINOWITZ ..... <i>Arb. a. d. Path. Inst., Berlin, 1906</i>	....	....	2	1
WESTENHOFER ..... <i>Berl. klin. Woch., 1903</i>	....	....	1	...
EBER ..... <i>Beit. z. Klinik d. Tuberkulose, 1905</i>	....	....	2	....
FIFE AND RAVENEL ..... <i>Proc. Phila. Path. Society, 1905</i>	....	...	1	....
Totals.....	18	9	41	3

\* In one case not included in the Table, both types were isolated from the mesenteric glands. In two cases in the Table, a bacillus of different type was found elsewhere than in the mesenteric glands.

<sup>o</sup> Including cases 4, 5, 6, 7, 8, 11 and 12 of authors.

pulmonary, intestinal, glandular, bone and other infections, can finally throw light upon the relative incidence and importance of these two groups of tuberculosis. As yet we have no data based upon such a series of cases. Both Commissions have selected too many instances of abdominal tuberculosis to make their results of value from this point of view. The significance of their investigations lies in other directions. However, the fact that 62 per cent. of intestinal or mesenteric gland tuberculosis proved to be of bovine origin is worthy of note. It means that the tubercle bacillus of cattle is a factor that can not be disregarded, as Koch maintains, in its pathogenicity to man. Again, when this 62 per cent. is compared to the percentage of bovine infection which has been demonstrated in other organs of the body, it emphasizes the fact that the mesenteric glands form the chief portal of entry for the bovine bacillus, with the tonsils alone to share this distinction.

The next point which compels notice is that of these seventy-one cases only twelve occurred in adults. The significance of these figures is somewhat dimmed by the fact that the glands of children were especially selected for the investigations. Nevertheless, although this may not be the correct ratio, all autopsy records show the marked preponderance of mesenteric gland tuberculosis in children as compared to adults. The statistics are absolutely sufficient, however, if we consider children and adults separately in two distinct groups and compare the proportion of human and bovine infection in each. Such a comparison reveals that of the fifty-nine cases in children, forty-one were bovine infections, some showing an atypical strain of bacillus; whereas of the twelve adult cases only three were of bovine origin. This difference in the type of infection can not be due solely to increased exposure on the part of young children to food contaminated with bovine bacilli, such as infected milk, for adults in the course of many years must be similarly exposed. We must attribute this difference either to a diminished natural resistance on the part of the child, in the nature of an increased permeability of the intestine, or to a lack of protective power of



the lymph nodes, or we must concede a degree of acquired immunity towards bovine bacilli on the part of the adult.

When we inquire into the course of the disease produced by the two types of bacilli in mesenteric gland tuberculosis, we find no points of differentiation. In either case the disease is generally progressive. However, instances of limited infections occur in each variety and are encountered generally when the tuberculous lesion is of secondary importance, the cause of death being some other infectious disease. For example, the bovine type has been found in a solitary calcareous node,<sup>3</sup> and again in the ascitic fluid of a patient who recovered and was well three years later.<sup>4</sup>

As regards the character of these lesions, Baumgarten has claimed that the human type of bacillus more commonly causes caseation, whereas the bovine organism incites calcification. Viewed from this standpoint, the seventy-one cases show no distinctions. Caseation was found in all but four instances, and these were of the human variety. Whether calcification develops probably depends more upon the virulence of the bacillus than upon its type, and also upon the peculiarities of its host. For instance, the second interim report of the British Commission shows that calcification was almost universally found in the mesenteric glands of swine, calves, and cows fed with human sputum, which may, I believe, be interpreted in this way. Finally, it should be mentioned that the German Commission reported that in seventeen cases of tuberculosis found at autopsy in children dying of acute infectious diseases, animal inoculation proved negative, in spite of the fact that tubercle bacilli were found in these nodes in eight instances, in some cases in exceptionally large numbers. This emphasizes the limitation of animal inoculation and the necessity of microscopical examination in the diagnosis of tuberculosis. It, furthermore, shows the resistance of children to tuberculous infection, and their ability to arrest the disease by killing the invading bacilli.

The cases which I shall now report, three in number, are all instances of primary mesenteric gland tuberculosis.

*Case 1.*—A. C. A child three years and nine months old,

admitted to the New York Foundling Asylum for malnutrition. No history was obtained. The autopsy, performed January 23, 1907, by Dr. Howland, who kindly sent me the pathological material, disclosed the following unexpected anatomical conditions: enlargement of the follicles in the lower portions of the small intestine, marked prominence of Peyer's patches, with three or four deep transverse ulcerations, enlargement and caseation of the mesenteric glands, moderate enlargement of the spleen. The lungs were negative; the mediastinal glands slightly enlarged. Pathological diagnosis: Tuberculosis of the intestine and mesenteric glands.

Smears made from the cheesy mesenteric glands showed a few tubercle bacilli. No bacilli were seen in smears from the small, slightly anthracotic bronchial glands. On January 25, two guinea-pigs were inoculated subcutaneously with bits of mesenteric gland, and one with bronchial gland tissue. Twenty-one days later, the pigs inoculated with mesenteric gland tissue were chloroformed, as they showed enlargement of the inguinal glands, although they had both gained slightly in weight. Both were found to be tuberculous. Tissue from the inguinal glands, iliac glands, and spleen was used for culture on dog serum and egg media. The pig inoculated with the bronchial gland was chloroformed after thirty-four days and showed no tuberculosis. Cultures were readily obtained from the spleen and inguinal glands; they grew after twenty-three days on the serum and later on the egg media. They appeared as round colonies at the upper part of the tube where the media was in an extremely thin layer. Later they spread out in heavy membranes. The bacilli were in the form of straight rods from 1.5 to 2 micra in length, and were similar in all the tubes. In subsequent cultures they varied considerably in length and contour. Thus in facility of culture and in morphology they resembled the human type. Intravenous inoculations into rabbits confirmed this opinion. For this purpose, 0.5 c.c. of a suspension of bacilli in salt solution corresponding in density to a twenty-four hour bouillon culture of typhoid bacilli was employed. As the table shows (Table II), the

bacilli possessed but slight virulence towards rabbits, causing only lesions after a period of two and three months. Bovine bacilli when thus inoculated invariably produce a generalized tuberculosis.

*Case 2.*—P. H. A twenty-two months old infant was admitted to the Babies' Hospital, in the service of Dr. Holt, to whom I am indebted for the following information. The family history showed that the father had suffered from a cough for an indefinite period. The child was nursed for four months and then fed on raw milk mixtures. It had a previous history of pertussis and measles, and had been in the hospital twice before, once suffering from an "acute gastro-intestinal toxemia," the second time from "bronchitis and anemia." It was now admitted on account of diarrhea.

Examination showed the baby prostrated, abdomen lax, and glands not palpable, except those in the inguinal region which were the size of shot. The temperature on admission was  $104.3^{\circ}$  F., weight 21 lbs. 10 oz. A diagnosis of tuberculous enteritis was made. Delirium soon supervened and was followed by death.

The autopsy, performed on September 3, 1906, by Dr. Martha Wollstein, whom I have to thank for the pathological material, revealed the following conditions: tuberculosis of the intestines and mesenteric lymph nodes, fatty liver, splenic tumor. Lungs and bronchial lymph nodes negative. Cultures of the heart's blood showed no growth. Sections of the spleen, liver, lung, ileum and mesenteric lymph nodes were made. On microscopic examination the liver, lung, and intestine showed no tuberculosis. In the spleen there were many young tubercles. The mesenteric glands showed numerous giant cells with peripherally arranged nuclei, as well as large areas of caseation.

From this autopsy, a piece of liver which appeared normal, bronchial glands of a deep red color and slightly enlarged, but otherwise negative, and a few large cheesy mesenteric glands were sent to me. Bacilli, many of them long and of beaded appearance, were found on the smears from the mesenteric glands. Five guinea-pigs were at once inoculated subcutaneously, one

with liver tissue, two with bronchial, and two with mesenteric gland tissue respectively. Of the five, the only one to develop tuberculosis was one of those inoculated with mesenteric gland. The autopsy of this pig showed nothing requiring mention except marked enlargement of the retrosternal lymph node. This lesion was found in other pigs often when there was but little tuberculous involvement of the lungs or surrounding tissues.

Cultures were made as in the previous case, but owing to a mishap no growth resulted; so that new cultures were made from a pig which had been inoculated on November 8 with some incubated tissue. In twenty-one days, discrete colonies appeared upon one egg and one dog serum tube, and soon became confluent and heavy. The individual bacilli were slightly curved and varied in length from 1.5 to 2.5 micra. Virulence tests made with the second and third generation of bacilli, as shown by the table, proved this strain to be of virulence similar to that isolated in Case 1. The reaction test on glycerin bouillon confirmed the conclusion that we were dealing with a bacillus of the human type. When inoculated, the bouillon was 2.1 per cent. acid to phenolphthalein, and eighty-two days later it was found to be 2 per cent. acid. According to this culture test, devised by Theobald Smith,<sup>5</sup> bovine bacilli when grown upon acid glycerin bouillon tend to bring the media towards the alkaline reaction, whereas in human cultures the reaction curve, although at first "moving toward the neutral point, soon swings back to a greater acidity."

The father of this child is now strong and healthy, and does not cough. As the infant had been fed on raw milk we might have been inclined, judging from the history alone, to consider this a case of bovine infection.

*Case 3.*—W. M., a boy seventeen years of age, was admitted to the service of Dr. Gilman Thompson at Bellevue Hospital. His family and previous history gave no indication of tuberculosis. At the time of admission to the hospital, he complained of abdominal pain and diarrhea of three months' standing, accompanied by marked loss of weight and strength.

Examination showed the boy's general condition to be poor.



A few râles were heard in the lungs. The abdomen was held rigid and was generally tender; percussion elicited dullness in the flanks, changing with change of position. The diagnosis was chronic pulmonary tuberculosis, tuberculous peritonitis, and tuberculous enteritis. Death followed four days after admission.

The autopsy performed three hours after death by Dr. Norris, who kindly furnished me the material for examination, disclosed the following pathological conditions: primary acute tuberculous hyperplastic enteritis, acute suppurative peritonitis, intestinal flora on smears, perforation of ileum, acute serofibrinous pleuritis, acute parenchymatous nephritis and hepatitis, suppurative sphenoiditis and otitis media, persistent thymus, bronchial lymph nodes slightly anthracotic, otherwise negative, mesenteric nodes enormously enlarged, most of them hyperemic, the largest showing on section yellowish areas of necrosis.

The large mesenteric glands, which were sent to me on April 15, 1907, were not typically tuberculous on macroscopic examination, resembling somewhat sarcomatous glands. A long search revealed a few acid-fast bacilli. Microscopic examination showed caseation in some sections, in others only a marked swelling and proliferation of the endothelial cells lining the perifollicular spaces. As in the other cases, passage through guinea-pigs was used to obtain pure cultures, bits of glandular tissue being inserted into subcutaneous pockets in the abdominal wall. In this instance both animals died after five days, so that the inoculation of two pigs was repeated with tissue thoroughly washed in salt solution. Both pigs gained in weight, but showed marked enlargement of the inguinal glands. They were chloroformed on May 5, 1907, twenty-three days after inoculation. Cultures were obtained from the inguinal and iliac glands. The growths were profuse and glistening and were successfully transferred to glycerin bouillon. The bacilli resembled those isolated in Case I, and were mainly straight rods, 1.5 to 2. micra in length, a few being longer. A suspension inoculated into the ear veins of two rabbits proved this strain to have a low virulence.



TABLE II.

Data of Inoculation of Rabbits with Pure Cultures of Tubercle Bacilli.

	Total Age of Culture	Number of Trans.	Age of Culture	Amount Inoculated	Number of Rabbit	Date and Method of Inoculation	Result	Remarks
Foundling Asylum	44 days	2	11 days	0.5 c.c.	250	3-31-'07 Ear vein	Chloroformed, June 9 (2 mos. 9 days)	A few foci in kidneys and anterior part of lungs
	44 days	2	11 days	0.5 c.c.	217	3-31-'07 Ear vein	Chloroformed, July 6 (3 mos. 6 days)	Foci in kidneys
Babies' Hospital	37 days	2	10 days	0.5 c.c.	213	1-12-'07 Ear vein	Chloroformed, Feb. 6 (2 mos. 20 days)	Extensive tuberculosis of lungs
	37 days	2	10 days	0.5 c.c.	267	1-12-'07 Ear vein	Chloroformed, Feb. 17 (3 mos.)	A few foci in lungs and kidneys
	53 days	3	12 days	0.5 c.c.	299	1-10-'07 Ear vein	Chloroformed, Apr. 18 (3 mos. 2 days)	Tuberculosis of iris. Foci in kidneys and lungs
	27 days	1	27 days	0.5 c.c.	208	6-5-'07 Ear vein	Chloroformed, Aug. 5 (2 mos.)	Two foci in lungs; a few in kidneys
Bellevue Hospital	27 days	1	27 days	0.5 c.c.	209	6-5-'07 Ear vein	Chloroformed, Aug. 5 (2 mos.)	Large foci in kidneys

*Summary.*

A review of cases of primary mesenteric gland tuberculosis in which the type of bacillus has been differentiated shows that over 60 per cent. have been caused by the bovine type of bacillus.

Among children the bovine infections greatly prevailed, whereas in adults, infections with the human variety were in the majority.

No pathological or clinical differentiation of the two forms of tuberculosis is as yet possible.

In children, as well as in adults, bovine or human tuberculosis may become limited and healed, and the bacilli may die.

It is interesting to note in contradistinction to the above statistics that the three cases reported by me were all of the human type.

*Bibliography.*

- 1 RAVENEL. *Amer. Jour. Med. Sciences*, 1907.
- 2 HESS. *Archives of Pediatrics*, 1907, June.
- 3 RABINOWITZ. *Berl. klin. Woch.*, 1907, No. 2.
- 4 DAMANN AND MÜSSEMEIER. *Untersuchungen über die Beziehungen zwischen der Tuberkulose der Menschen u. d. Tiere*. Hanover, 1905.
- 5 SMITH. *Jour. Med. Research*, xiii, No. 3.

---

A CASE OF SYPHILITIC INTERSTITIAL SPLENITIS  
WITH GENERAL AMYLOID DISEASE; A CASE  
OF HYPERNEPHROMA WITH EXTENSIVE  
METASTASES IN THE LUNGS.

H. MARTLAND, M.D.

The first specimen which I have to present is a spleen which shows a rare and, at the same time, a rather typical lesion; namely, a marked cirrhosis of syphilitic origin. The organ was removed from a woman, fifty-four years of age, who died on the

medical service of the City Hospital after having been under observation for about two weeks. On admission to the hospital she stated that she was a domestic and gave as her chief complaint vague stomach trouble.

Physical examination revealed a poorly nourished woman, who appeared markedly anemic. Her teeth were very bad; her tongue was coated, and showed a slight tremor. The heart was slightly enlarged, being beyond the nipple line; a systolic murmur was heard at the apex, and over the aortic-area. The second aortic sound was accentuated. The pulse was full and regular. On palpating the abdomen, the liver was felt a hand's breadth below the costal margin, its edge being firm and rounded. There was slight tenderness over the epigastrium. The abdominal veins were prominent. The remainder of the examination was negative. The urine was amber, acid, 1.010. Albumin, and hyalin and granular casts were present.

The blood count showed the following:

Erythrocytes	.....2,384,000
Hemoglobin	..... 15 per cent.
Color index	..... 0.3
Polymorphonuclears	..... 87 per cent.
Large lymphocytes	..... 4 per cent.
Small lymphocytes	..... 9 per cent.

While in the hospital, the patient's temperature was always about normal. The pulse varied from 68 to 108, usually it was around 90. The respirations were increased only at the time of death. The blood pressure varied from 90 to 130. The chief subjective symptoms were nausea, vomiting and diarrhea. She gradually grew weaker, becoming irrational and incontinent. During the last few days there was a marked diminution in the amount of urine secreted. She died of air hunger (probably anemic in origin).

The clinical diagnosis was: Severe secondary anemia, cause undetermined; cardiac hypertrophy; arteriosclerosis; chronic nephritis.

In regard to her previous history, it is noteworthy that she

had contracted syphilis when thirty years old, and had received very little treatment. Three years later she had an operation on the rectum (probably for stricture). When forty years old she was in the City Hospital with a severe gastritis.

The summary of the autopsy findings is as follows: General amyloid infiltration of the spleen, liver, kidneys, adrenals, mesenteric glands and intestine; syphilitic interstitial splenitis; chronic interstitial nephritis; chronic interstitial myocarditis; pulmonary edema; and smooth atrophy of base of tongue.

The spleen was quite large; it weighed 870 grams and measured 17x12x9 cm. It was oval in shape and presented a notched anterior border. What impressed one at the time of the autopsy was its great firmness; on section it cut with difficulty, the knife encountering firm, cartilaginous masses and areas of calcified tissue near the hilum: the cut section was a light ham-red color. The capsule was only moderately thickened, and free from perisplenitis. The splenic substance presented a rather unusual appearance, most marked at the hilum. Here the trabeculae were enormously thick, being 2, 5 or 10 mm. across; they were a pale bluish white, and had a peculiar hyalin, semitranslucent appearance. These bands divided the spleen into small and large, irregular islands of spleen pulp. The large vessels, when cut transversely, showed thick walls with a glistening appearance. The general color of the spleen pulp was light red; but in places near the trabeculae a very dark red color was seen. The Malpighian follicles were hardly visible.

On staining with a dilute iodine solution, the surface presented numerous dark mahogany-brown points, most of which represented the regions of the arteries of the Malpighian corpuscles. Sections stained with methyl violet showed a diffuse amyloid infiltration, a rose-red homogeneous substance appearing in and around the arteries of the Malpighian follicles, in the capillaries of the spleen pulp, and in the walls of the cavernous sinuses. The deposition of the amyloid material was rather irregular; although diffuse, it was not massive.

Sections stained with the eosin-hematoxylin and Mallory's

anilin blue methods showed enormously thickened trabeculae, which were composed of a poorly nourished, not cellular, hyalin connective tissue. The reticulum supporting the spleen pulp was greatly thickened, and there was a great waste in the splenic substance. There was also marked atrophy of the lymphoid mantels, the central artery appearing bare in many places.

In other words, we have to deal here with an extensive cirrhosis of the spleen. If we look for the cause, there can probably be no question that it was of syphilitic origin; in favor of this is the extent and distribution of the lesion, which was most marked around the hilum; the appearance of the tissue itself, the presence of thick isolated bands of connective tissue, similar to those seen in syphilitic cirrhosis of the liver, the affection of the blood vessels, the amyloid degeneration (which in this case must be attributed to syphilis), and the certainty of syphilis as an etiological factor.

The liver showed extensive amyloid infiltration; the liver cells were markedly atrophied, due both to pressure and to an anemia caused by the presence of the amyloid material. The kidneys showed marked interstitial nephritis with extensive amyloid infiltration of the capillaries of the glomeruli and the straight vessels of the cortex and medulla.

The second specimen presented, a large hypernephroma of the right kidney, is interesting because it represents a type of these tumors which is made up of polymorphous cells, part of which bear a close resemblance to those of the medulla, while others are more typical or cortical cells. On the other hand, the metastatic nodules seem to be made up almost entirely of more typical cortical cells.

The patient was a colored man, sixty years of age who was under observation at the City Hospital for seven weeks. He was admitted complaining of vague rheumatic pains and a slight cough, which he had for some time. On admission, fluid was found in his right chest, and on aspiration 1,000 c. c. of clear serous fluid was obtained. The greater part of his abdomen was occupied by what appeared to be an enlarged liver, the lower edge



being felt almost down to the brim of the pelvis, in the median line, at the navel, and on the left side, to two inches below the costal margin. He also had prominent abdominal veins and varicose veins of the legs. Three days after admission, while going into the bathroom, the patient fell, striking his head and back. Soon after this fall he suddenly developed a severe dyspnea, which did not leave him until the following day. Six weeks after admission, fluid was again found in his right chest, and 2,500 c.c. of a bloody fluid was aspirated. One week later he died from an attack of pulmonary edema. The temperature never rose above 100°; pulse rate was 78 to 90. Blood pressure on admission was 210, but was not taken again. The urine was amber, acid, 1.017, and contained a large amount of albumin, leucocytes, red blood cells, and hyalin and granular casts. The blood count was negative.

Autopsy showed a large encapsulated hypernephroma of the right kidney; hypernephroma of the right adrenal; multiple cortical adenomata of the left adrenal; hematogeneous metastases in both lungs; hemorrhagic pleurisy; smooth atrophy at base of tongue; and stasis in all viscera.

The hypernephroma weighed 3,210 grams, measured 27x19x14 cm. and was well encapsulated. It was composed of three distinct parts. Near the upper pole and near the median line, was a separate mass, 10x11 cm. in diameter, entirely separated from the surrounding tumor by dense connective tissue. It had the same structure as the large tumor and probably represented a hypernephroma of the right adrenal, since this organ could not be found in its anatomical position. To the outer side of this adrenal tumor, and forming the upper portion of the large tumor, was seen a shell of kidney substance, representing the upper pole and upper half of the lateral margin of the kidney; this was composed almost entirely of kidney cortex. The main tumor mass presented the appearance of an ordinary hypernephroma; it was made up of round or oval masses, varying in size and separated by connective tissue; each mass was divided into smaller areas with a small amount of connective tissue around them.

The various display in colors seen was to be attributed to the extremely fatty, hemorrhagic and necrotic areas commonly found in these tumors. The pelvis of the kidney was comparatively free from tumor growth. The tumor cells had, nevertheless, invaded the renal veins; and in the inferior vena cava, at the insertion of the renal vein, was seen a large thrombus, almost occluding the vena cava. This thrombus was composed entirely of cells resembling those in the zona fasciculata of a normal adrenal. The metastases in the lungs were also composed of tumor cells.

With regard to the tumor itself, we have then to deal with what is commonly called an atypical hypernephroma: that is, one which is made up of cellular elements which appear to be derived from the medulla and partly from the cortex. The cells resembling those of the cortex are large polyhedral cells, containing round or oval, deeply staining nuclei. The cytoplasm (in sections which have been passed through alcohol) shows as a clear vacuole, containing a distinct limiting membrane and a little granular debris. They are situated in alveoli which are formed by naked capillaries. The cells simulating those of the medulla are smaller than the cortical cells; they are polyhedral in shape, with faintly staining nuclei, and a finely granular vacuolated cytoplasm. They are contained in alveoli which are formed by coarse reticulum bearing a structure similar to the reticulum of the normal adrenal. The lungs showed a diffuse hematogenous infiltration of cortical cells, the cell nests springing from the alveolar capillaries and growing into the alveoli.

I wish, also, briefly to call attention to the following conditions observed in the histological study of this tumor. The capsule is composed of dense fibrous tissue with a few scattered elastic fibers. It is not very cellular and contains very few blood vessels. In this capsule, surrounded by the fibrous tissue, are numerous collections of small round cells. These cells are mononuclear, with dark staining nuclei and a very scanty protoplasm. They are very decidedly embryonic in appearance. These cell groups seem to invade the interior of the tumor, where occasionally pictures are observed which may be interpreted as rep-

representing the transformation of these cells into those resembling the medullary cells. It has been held that such cell groups represent immature and embryonic medullary cells.

The capsule and the large trabeculae also contain many epithelial lined tubules. These tubules are elongated, having a distinct basement membrane, and are lined with cuboidal epithelium. They look distinctly embryonic and are supposed by some to be remnants of the Wolffian body (as persistent Wolffian tubules have been recognized in adrenal rests). Others think that they are renal rests which have become included in the tumor mass, and have assumed an embryonic appearance from the pressure of the surrounding connective tissue—a condition which does not stand without analogy, since we know that indurations or replacement of parenchyma by a foreign invasion is not infrequently followed by a return to embryonic forms in the essential parts of the parenchyma. This, for instance, is the case in a slowly progressive indurative tuberculosis of the lungs. We have often observed a hyalin matter very similar to hyalin casts in the lumen of these tubules.

As to how far a division of this tumor into portions resembling the various types of the normal adrenal cells may be justifiable, I shall not attempt to discuss here on account of the uncertainty concerning this problem.

---

## THE ACTION OF BILE ON THE PNEUMOCOCCUS, STREPTOCOCCUS, AND STREPTOCOCCUS MUCOSUS.

E. LIBMAN, M.D., AND J. ROSENTHAL, M.D.

(Presented by Dr. Rosenthal.)

Our object this evening is to give a description and a demonstration of the lytic action of bile on the above-named organisms. Our presentation is a part of a study which we have undertaken concerning the identification of these organisms.

Neufeld, in 1900, while working on some problems in immunity found that if 0.1 c.c. of rabbit bile is added to 1 or 2 c.c. of a bouillon culture of pneumococci, lysis occurs, the culture clearing in from ten to fifteen minutes. This result was produced more or less by human bile as well as by the bile of monkeys, guinea-pigs, dogs, cats, oxen, and goats. The phenomenon occurred as well at room temperature as at incubation temperature. Boiling the bile had no effect on the result, but freezing retarded the action. If hanging drops were made it was found that the chains became fewer and shorter, the individual shorter and then indistinct, and in a few minutes no remains of the organism could be seen.

Neufeld further found that "crystallized bile," prepared by precipitating with ether an alcoholic extract of bile, also had this lytic effect. This crystallized product, when free from coloring matter, consisted chiefly of the bile salts, and these, in turn, were found to possess the lytic power over pneumococci and *Streptococcus mucosus*.

From 1900 to 1907, no further work was done on this subject. In 1907, Levy of Berlin proposed to use Neufeld's observations as the basis for a differential test between pneumococci and streptococci. Neufeld himself had not suggested the diagnostic value of the test. Levy confirmed Neufeld's observations after testing five strains of pneumococcus, six of *Streptococcus mucosus*, and twenty-four of streptococcus. He used sodium taurochlorate in a 2.5 per cent. solution, and found that it had a bacteriolytic action on pneumococcus and *Streptococcus mucosus*.

His procedure was as follows: He added a 5 per cent. solution of the salt dissolved in nutrient bouillon to an equal amount of the twenty-four-hour culture of the organism to be tested. As a control, he used an equal amount of the same culture and sterile bouillon. With pneumococcus he obtained complete lysis.

Mandelbaum of Munich followed up Levy's work. He used a 10 per cent. solution of sodium taurochlorate in nutrient bouillon. He tested eight strains of pneumococcus, four strains of *Streptococcus mucosus*, and fifteen strains of streptococcus. To

the twenty-four-hour bouillon cultures of the above strains he added an equal amount of the 10 per cent. solution of the bile salt. Cultures of pneumococci and of the *Streptococcus mucosus* cleared up rapidly, while cultures of streptococci remained clouded. He found that although streptococci were not dissolved by this solution, they were injured, so that on transplanting to agar plates no growth was obtained. In hanging drops made from the pneumococcus cultures to which the bile salt had been added, he found a few involution or degenerate forms of the organism. Careful examinations were necessary to find these forms. They were usually found by looking at the periphery of a hanging drop, cutting down the light, and allowing a little Loeffler's methylene blue to run under the cover slip. Remains of the pneumococcus and *Streptococcus mucosus* could be found after two days. Thus he demonstrated that with the bile salt there was not complete lysis; yet after inoculation on agar plates no growth was obtained.

Mandelbaum also made some experiments with animal bile. He recommends ox-bile as it is easier to get, is inexpensive, and mixes well with the cultures. He used 2 c.c. of bouillon culture and 0.5 c.c. of ox-bile. He found that this had a better action than the bile salt and lytic action was complete. At the end of an hour no traces of the organisms could be demonstrated even after staining.

We considered it advisable to take up this study because for several years we have had a method of classification of the organisms in question based on certain observations made by Dr. Buerger, Dr. Hiss, and one of us (Libman). The authors, with perhaps the exception of Levy, did not state distinctly how they classified their organisms, and we therefore thought it was advisable to see how the bile would act on organisms which we have been classifying as pneumococci and streptococci. We have studied ninety-nine organisms: sixty-eight streptococci, encapsulated and non-encapsulated; nineteen pneumococci; and twelve strains of the *Streptococcus mucosus*. In every instance in which we have classified organisms as pneumococci and as the Strep-



tococcus mucosus, the organisms were dissolved by bile, and we are, therefore, in a position to confirm strongly the work of the previous writers. The clearing of the cultures of the pneumococci usually occurred within a few minutes; in only one instance did we have to wait twenty minutes. The *Streptococcus mucosus* cultures usually cleared within a minute. In our work we used ox-bile, adding 1-4 or 2-5 bile to the bouillon cultures. The cultures were made in five bouillons, as follows:

- 1 Neutral phenolphthalein with 1 per cent. pepton.
- 2 Neutral phenolphthalein with 2 per cent. pepton.
- 3 One-half per cent. acid with 1 per cent. pepton.
- 4 One-half per cent. acid with 2 per cent. pepton.
- 5 Two per cent. glucose bouillon, 1 per cent. acid.

We used these various bouillons to determine which could give the best growths of pneumococcus because at times certain organisms would hardly grow at all. In previous studies and in those now reported, we found that neutral bouillon gives a better growth than acid bouillon.

The bile was usually added to twenty-four-hour cultures. Hanging drops were made and in only a few instances could the remains of any organisms be seen after a short while. The cultures were then allowed to stand at room temperature for a length of time varying between five and twenty-four hours, and inoculations were made on blood agar, according to the method of Drs. Bernstein and Epstein. From the streptococcus cultures to which bile had been added, we were able in every instance to obtain a growth. We recovered the pneumococcus nine times, and the mucosus three times. Thus it is seen that the lytic action is often not complete.

The fact that Mandelbaum obtained no growths from the streptococcus cultures to which bile had been added, is due to the fact that he did not use an optimum medium like blood medium, but did use agar.

It is important to know that the presence of serum or of glucose interferes with the occurrence of the reaction. Nicolle and Adil-Bey pointed this out. They attempted to explain the

interference of the sugar as being due to the fact that the acids produced by the organisms will precipitate the bile salts and thus prevent lytic action. They also found that the addition of certain salts (particularly magnesium sulphate) augments the lytic effect.

We succeeded in causing lysis in glucose bouillon cultures, twice with strains of streptococcus, and three times with the pneumococcus. For diagnostic work, however, the use of glucose bouillon is distinctly disadvantageous.

From what we have said it is readily seen that we have in the bile test a very valuable method of differentiating pneumococci and streptococci. The *Streptococcus mucosus* is so readily recognized by its morphology that there is no difficulty in distinguishing it from the pneumococcus in early cultures. Our experience leads us to believe that the presence of the type capsule of the pneumococcus and *Streptococcus mucosus*, as described by Dr. Buerger, and the solution by means of bile are the best methods to be used in attempting to identify pneumococcus and streptococcus.

The value of the type capsule of the pneumococcus for diagnosis is demonstrated by the fact that in every instance in which the type pneumococcus is present, the organism is promptly dissolved by bile. In a later paper we shall present the results of our studies with inulin, the precipitation test and blood media.

Note:—Since this paper was presented to the Society we have made some experiments with taurocholate of soda and have been able to confirm the statements made by previous authors. This salt is somewhat slower than the bile in producing the lytic effects and is expensive. There is no advantage, as far as we can see, in its use.

### *Discussion.*

DR. E. LIBMAN said that this study had been taken up for a particular reason. As had previously been pointed out, it was known that pneumococci may in the human body become very much altered and acquire some of the characteristics of the streptococcus. There were no methods at our disposal to distinguish such changed pneumococci from streptococci, and this study was

undertaken to find out whether bile would dissolve pneumococci so changed in the body. It had been found that bile will dissolve pneumococci which have obtained some of these peculiar characteristics. So that it looked at present as though solution by bile was the most reliable method we have now to differentiate these organisms.

### ECHINOCOCCUS CYST OF THE LIVER WITH RUPTURE INTO THE DUCTS; CHOLANGITIS; CHOLECYSTITIS; PNEUMOCOCEMIA.

BY E. LIBMAN, M.D., AND B. CROHN, M.D.

(Presented by Dr. B. Crohn.)

The patient from whom these specimens were obtained was a female, aged thirty-two, who was admitted to the Mt. Sinai Hospital in the service of Dr. Gerster, March 2, 1908. The history was rather difficult to obtain as the patient spoke Hungarian only.

*Abstract of History.*—This is the patient's third attack of pain. The time of the original attack is not known; the second attack occurred about three months ago. Four days before admission the patient had severe pain in the right hypochondrium. There were vomiting, fever and frequent chills. These symptoms have persisted until the present time. The patient was jaundiced yesterday for the first time. She is in the fourth month of pregnancy.

*Examination on Admission.*—There is distinct icterus present. The liver extends to a hand's breadth below the free border and is very tender. Just to the right of the umbilicus there is an indefinite mass corresponding apparently to the gall-bladder.

Unfortunately no blood count was made, but the spreads of the blood showed no increase in the number of eosinophiles.

The patient was operated upon by Dr. A. A. Berg on the day of admission. The liver was found enlarged and congested. The gall-bladder was distended, tense, reaching down a few

inches below the liver. The gall-bladder was aspirated and about ten ounces of pus were removed. Cholecystectomy was then performed. No stones were found. The wound was drained.

On the evening of March 2, the patient aborted. On March 3 there was repeated vomiting. The vomiting continued; the pulse became progressively more feeble and the patient died. On admission the temperature was about  $102.6^{\circ}$ , and remained about the same until it rose to  $105^{\circ}$  shortly before the patient died.

The autopsy was performed on March 5. The important findings were, in brief, as follows:

There was a general fibrinous peritonitis in the upper part of the abdomen on the right side. The spleen was about one and one-half times normal size; pulp rather congested and soft. There were hemorrhages in the mucosa of the stomach. The most interesting findings were in the liver. In the extreme left part of the left lobe of the liver there was present a suppurative echinococcus cyst about the size of a small orange. Over it there was perihepatitis with fairly firm adhesion to the abdominal wall. An old perforation, admitting a lead pencil was found leading into the gall ducts. All the gall ducts in the liver were distended, contained pus mixed with bile and in some of them cysts were found. In the common bile duct there was found a large cyst. At the papilla there was a plug of mucus. There were no unusual appearances in the part of the liver from which the gall-bladder had been removed. There were present some recent thrombi in some of the larger branches of the portal vein in the liver. In some places the thrombi extended into the smaller vessels.

*Bacteriological Examination.*—The cultures from the material removed from the gall-bladder during life showed a pure culture of pneumococci. A blood culture was made two days after the operation, 7 c.c. of blood being used. There were thirty-one colonies of the pneumococcus to the cubic centimeter of blood. Pneumococci were also found in the blood in a culture made at the post-mortem examination.

The pus in the cyst of the liver showed pneumococci almost

exclusively, and in the ducts there were found pneumococci and colon bacilli.

The case was therefore one of echinococcus cyst of the liver with perforation into the ducts, suppurating cholangitis and cholecystitis due to pneumococci and resulting general infection. The case is certainly of great interest considering that the clinical picture at the time of admission to the hospital was simply that of cholecystitis. It has been known that cases of hydatid cysts of the liver could give the clinical picture of gall-stones, because of cysts being discharged through the bile ducts. This case is of still greater interest. In it the clinical picture before the last attack was the same as that of gall-stones, the attack being due to passage of cysts through the ducts, but in addition was typically that of cholecystitis, and such was even the post-operative diagnosis. The pus from the gall-bladder contained no hooklets and no scolices, so that it was not possible to suspect the true character of the disease until the time of the post-mortem examination.

The frequency with which rupture of hydatid cysts into the gall-ducts occurs is not definitely known. Rolleston states that if the communication between the cyst and the bile-duct is small, the fluid in the cyst may run quietly away, or on the other hand, the cyst may be infected from the bile duct and suppurate. The characteristic cases are those in which the communication between the cyst and the duct is sufficiently large to allow the daughter cysts to escape and cause colic and jaundice from biliary obstruction. Rolleston believes that the hydatid cyst may irritate the mucous membrane in virtue of toxic bodies developed in the contents of dead cysts and set up a descending cholangitis. But in most cases he believes that the cholangitis is due to bacterial infection, very possibly ascending from the duodenum. The infection may spread into the cyst and cause suppuration. In our case the infection probably occurred in this manner, although one can not definitely exclude a hematogenic infection. Rolleston says that such infections have occurred in the course of typhoid fever, infective endocarditis and the puerperium.



We believe in our case that the pneumococcemia was most likely secondary. In our experience we have not found general infections in cholecystitis except when accompanied by cholangitis. There is therefore no reason why the pneumococcus infection in this case may not have been due to the cholangitis, although, as stated above, a hematogenic source of the infection can not be excluded. If the infection were hematogenic, we would, of course, believe that the infection occurred a long time after the rupture of the cyst into the duct because the opening of the channel leading into the duct was lined by smooth mucous membrane.

In some cases of suppurative hydatid cysts no bacteria were found in the pus. The organisms which have been found (citing from Rolleston) are streptococci, *Staphylococcus aureus* and *citreus*, the pneumococcus and *Bacterium coli*. When pus has a fetid odor, anaerobic bacteria are apt to be present.

## THE PATHOLOGY OF THE VESSELS IN CASES OF GANGRENE OF THE LOWER EXTREMITIES DUE TO SO-CALLED ENDARTERITIS OBLITERANS.

### Preliminary Communication.

LEO BUERGER, M.D.

The subject which I wish to discuss before you to-night is one which presents points of interest both to the clinician and to the pathologist. It is my purpose to give you a brief account of the pathology of the vessels in that rather unique set of cases of spontaneous gangrene which were first described by von Winiwarter. In 1879, this author published the results of pathological findings in a single case of gangrene of the leg in which he found an obliteration of practically all the arteries by a chronic proliferative process which, in his opinion, was due to a new growth of tissue from the intima. He therefore described the condition under a new name, "endarteritis obliterans."

Patients afflicted with this so-called "endarteritis obliterans" present a very varied complex of clinical symptoms which are so characteristic that the diagnosis of the condition is not difficult. We see these patients not infrequently in New York, particularly in the dispensaries and hospitals that treat the Polish and Russian Jews. In a general way, we may divide the symptoms into those which precede and those which accompany and follow the onset of gangrene. The disease usually occurs in young adults between the ages of twenty and forty; and it is because the gangrenous process may begin at an early age that the names "presenile" and "juvenile" gangrene have been employed. In one class of these patients we find rather characteristic attacks of ischemia. The patients complain of indefinite pain in the foot, in the calf of the leg, or in the toes, and particularly of a sense of numbness or coldness whenever the weather is unfavorable. Upon examination we find one or both feet markedly blanched, almost cadaveric in appearance, cold to the touch, with no pulsation in either the dorsalis pedis or posterior tibial arteries. When the feet become warm some color gradually returns. Another set of patients complain particularly of rheumatic pains referred mostly to the leg; others are able to walk but a short distance, for the advent of paroxysmal, shooting, cramp-like pains in the calf of the leg makes it imperative for them to stop short in their walk. Some of these cases give the typical symptoms of intermittent claudication. At times the first evidence of disturbance in an extremity is the appearance of a blister, a hemorrhagic bleb or an ulcer, near the tip of one of the toes, or under a nail, more rarely near the heel; and when this condition ensues, local pain becomes a prominent symptom. When trophic disturbances, such as bleb or ulcer, have once developed, we frequently find that the skin in the neighborhood becomes gangrenous and at this stage amputation is usually imperative because of the intensity of the pain and the progression of the gangrene. Many patients present a condition which simulates that described by Weir Mitchell under the name of "erythromelalgia." When the limb is held in a dependent position, the tips of the

toes become bright red, this color rapidly extending upward over the dorsum of the foot, sometimes only to the tarsus, sometimes to the ankle, or, rarely, even higher up. When the disease involves both extremities almost simultaneously, then the trophic disturbances, the ischemia, or the reddening, give rise to a symptom complex which is often diagnosed as Raynaud's disease. In short, after longer or shorter periods characterized by pain, coldness of the feet, numbness, ischemia, intermittent claudication, and erythromelalgic symptoms, evidences of trophic disturbance appear finally to pass over into a condition of dry gangrene.

### *Historical.*

Although the literature bearing upon the pathology of the disease just described is large, I wish to call attention to some of the more important contributions only. Von Winiwarter and Friedlander ascribed the closure of the vessels to a proliferation of the cellular and fibrous elements in the intima and therefore proposed to call the lesion by the name "endarteritis obliterans." This theory has been accepted by most authors, and even to-day it is to be found in all the text books. Somewhat later, Wilonski pronounced the opinion that the essential change in the vessel walls was due to a multiplication of the elastic fibers, and proposed the name "arteritis elastica" for the condition. Perhaps the most important contributions are those of Weiss and Zoege von Manteuffel, because these authors placed an entirely new interpretation upon the pathological findings. Basing his paper upon the studies of his assistant Weiss, von Manteuffel suggests that the extensive occlusion of the vessels in this disease is dependent upon a primary arterio-sclerosis; that the obliterative process commences in the popliteal artery where it owes its inception to the formation of a parietal white thrombus; and that, by virtue of a gradual extension of the parietal thrombi downward followed by organization, a picture resembling an obliterative endarteritis is produced. In his cases the veins do not seem to be involved in the process. Von Manteuffel comes to the con-

clusion that the thrombosis is due to desquamation of endothelial cells, and that this occurs where the intima shows the most advanced lesions of arteriosclerosis, namely, somewhere in the popliteal artery. In spite of the views expressed by these latter authors, Sternberg, from the study of eight cases, is in accord with the old conception first suggested by von Winiwarter. Bunge, on the other hand, agrees with von Manteuffel, but his three cases appear to be instances of advanced arteriosclerotic change in elderly people, rather than examples of the disease grouped under the name "endarteritis obliterans."

Two schools, then, have arisen among those who have made careful anatomical investigations; first, those who agree with von Winiwarter and who attribute the closure of the vessels to proliferation of the intima; and, second, those who consider the process to be a peculiar type of arteriosclerosis in which desquamation of endothelium in the popliteal artery leads to the formation of parietal white thrombi and to occlusion of the arteries by direct peripheral extension from the primary focus.

During the past year I have had an opportunity of observing quite a large number of patients suffering from this disease, both in dispensary practice and in Mt. Sinai Hospital, and, through the kindness of Drs. Lilienthal, Gerster, and Sachs, have been able to make careful anatomical studies on ten amputated lower extremities. Although the results of the macroscopical and microscopical examinations of the vessels agree in a number of essentials with the findings of other authors, certain additional facts were obtained which throw new light upon the genesis of the process. From my own findings, I may anticipate now by saying, I can agree neither with von Winiwarter nor with von Manteuffel, and must express the view that we are dealing here with *thrombo-arteritis* and *thrombo-phlebitis* followed by organization and canalization, and not with an obliterating endarteritis.

#### *Gross Pathology.*

It is not my purpose to give you a minute and detailed account of the pathological lesions which underlie the clinical pic-

ture that I have described earlier in my paper. At present, I am able to report to you only the changes in the vessels, and must defer the results of the examination of the nerves until another time. Sufficient data, however, have been collected by me to warrant the assumption of a new theory in regard to pathogenesis, and I shall therefore confine my remarks to those important gross and microscopical lesions which bear directly upon my own conception of the process, reserving a complete discussion of the etiological factors for a future publication.

If we dissect out the vessels in these cases we are struck by the fact that there is an extensive obliteration of the larger arteries and veins. Besides this we find two other lesions which vary greatly in their intensity, namely, the periarteritis and the arteriosclerosis.

Upon making a large number of sections through such obliterated arteries and veins at different levels, we find certain characteristic appearances, which, in a general way, depend upon the age of the occluding process. Usually the vessel is seen to be filled with a grayish or yellowish mass that can be distinctly differentiated from the annular wall of the vessel, and that appears to be pierced at one point (more rarely at a number of points) by an extremely fine opening through which a minute drop of blood can be squeezed. Such obturating tissue is firm in consistency and does not at all resemble the crescentic or semilunar occluding masses of arteriosclerosis. The vessel itself is usually contracted so that its wall appears somewhat thickened. This picture is characteristic of arteries or veins which are the seat of a very old oblitative process, and is to be found most frequently in the peripheral portions of the vessels, although at times this type of lesion may extend throughout the whole length of the vessel, from the dorsalis hallucis almost into the popliteal.

As we trace certain of the obliterated arteries or veins upward, we are apt to meet with a change in the character of the obturating tissue; frequently it becomes softer, and more brownish in color, and terminates abruptly in the lumen of an apparently normal vessel; at other times the brownish tissue gives



way to soft reddish masses which are evidently the results of recent thrombosis. In some cases this thrombotic process occupies large portions of the vessel's course; in others, it is of short extent and terminates in a long cone of recent thrombus

It is interesting to note that the veins share equally with the arteries in the lesion of occlusion. In some cases the veins are more extensively involved than the arteries and this is particularly true of the collaterals of the posterior tibial which are often closed when the anterior tibial veins are open. As for the arteries, we usually find an obliteration of a part or the whole of the anterior tibial, of the dorsalis pedis and dorsalis hallucis, and occlusion of the posterior tibial and plantar vessels with or without involvement of the peroneal. Sometimes the anterior tibial is practically normal in its upper half or upper two-thirds. More rarely a large portion of the dorsalis pedis is open with the beginning of the occlusion in the upper part of this vessel, or in the lower part of the anterior tibial. It is to be regretted that the termination of the process in the posterior vessels of the leg could not be determined in every instance because of the fact that amputation was done at a point where the posterior tibial was closed. In two cases, however, the popliteal and part of the posterior tibial vessels were found free; in others the popliteal could be felt to pulsate before the operation, and we can therefore conclude that in a number of cases at least the obturation does not attain the level of the popliteal artery.

Without giving a detailed description of the extent of the occlusion in all the cases, we may summarize by saying that we usually meet with obliteration of large territories with closure of the distal parts of the vessels, rather than the proximal; that there is often an involvement of some of the smaller branches such as metatarsal and tarsal; but that the finest arteries are free. The beginnings of the obliteration are not to be sought in the capillaries nor in the finest branches. If we follow the vessels upward, we frequently see a sudden cessation of the process, and, in a number of instances, we find that some five or ten centi-

meters of a vessel's length are closed, and that the portions above and below are apparently normal.

It is from a study of the terminations of the obliterating masses of tissue together with a study of those parts of the vessels which are apparently unaffected by the process, that most valuable information in regard to the pathology of the disease can be gained. As already indicated, there may be a sudden and abrupt change from occluded vessel to normal vessel, that is to say, the yellowish brown tissue terminates in a rounded dome-like process which projects into an apparently normal lumen; or there may be a transition into red thrombotic masses or a conversion of the denser occluding tissue into tissue not unlike granulations. Such terminations occur at various points in the course of the arteries and veins. In one case the obliteration of the anterior tibial extended to about the middle of its course and above this point its walls were almost normal save for some thickening of the intima. In another case the upper and lower terminations of the occluding tissue were found in the posterior tibial and in the peroneal arteries.

From the peculiar appearances presented by these terminations, from the apparently normal condition of the vessel above and below the occluding masses, and from the transition into thrombosed areas, it would appear that we are dealing with a thrombo-arteritis or thrombo-phlebitis, rather than with a proliferative or obliterating process derived from the intima of the arteries and veins. The microscopical studies gave sufficient evidence of the correctness of this conception.

Besides the lesion of occlusion there are two other striking changes, namely, a certain amount of arteriosclerotic thickening and periarteritis. The arteriosclerosis is never pronounced except in those rare instances in which the patient has suffered from the disease for many years and has reached the latter part of the fourth decade. As a rule, we note but a very slight degree of whitening or thickening of the intima here and there in the patent portions of the vessels. There were deposits of lime in but one case, and these were of but small extent.

A much more interesting and more important change is the fibrotic thickening of tissues immediately about the vessels, which I wish to group under the name "periarteritis." Wherever the vessels are occluded there is apt to be an agglutinative process which binds together the artery and its collateral veins, and sometimes also the accompanying nerve, so that the liberation of the individual vessels by dissection is difficult. This adhesive condition is due to fibrous tissue growth and varies considerably in its amount. At times we find little or no change about the occluded artery, at times fairly firm agglutination of the vessels in the sheath, without much fibrosis, and at other times so large an amount of connective tissue growth that isolation of the vessels or nerves becomes impossible, and the vascular structures make up one dense rigid cord. In a general way we may say that whenever both the collateral veins and the artery are occluded, we expect a fair amount of periarteritis, and that when but one vessel is affected the perivascular change may be insignificant; and, finally, that the amount of periarteritis varies in the different cases as well as in the different territories affected by the disease.

### *Histology.*

The pictures presented by the vessels involved in this process are so varied that I must needs confine myself to the description of those rather typical changes that have suggested the true nature of the process to me, and from a study of which we can see the development of the lesion from its incipency to its final maturation. I wish to point out, first, the lesions of arteriosclerosis; second, those that belong to periarteritis; third, the typical pictures found in the old obliterative process; fourth, the differentiation of this lesion from the occlusive changes of arteriosclerosis; and, fifth, the various stages in the development of the occluding process from the beginning of the thrombosis to the final filling up of the vessel with dense fibrotic masses.

Both the arteries and the veins show varying degrees of thickening of the intima, the usual subendothelial changes with a fairly well marked hypertrophy of the internal elastic lamina

without much proliferation of new elastic tissue in the thickenings of the intima. Of the two types of elastic tissue production pointed out by Jores, that which is dependent upon reduplication or hypertrophy of the internal elastic lamina is the more pronounced. Now and then in the older patients there are small plaques. Although the very small arteries may also be the site of thickening of the intima, this change is never sufficiently great to lead to complete or even marked obliteration of the lumen of the vessel. In the popliteal artery the formation of nodular thickenings is most extensive, but even here these are of moderate size.

The periarteritis manifests itself in a proliferation of connective tissue in and around the adventia, and is of two types, recent and old. Where the perivascular proliferation is active, the fixed connective tissue cells multiply and fibrous intercellular substance is deposited. Here and there small perivascular foci of lymphoid cells are found, but these do not seem to take an important part in the formation of connective tissue. In the old variety, the fibrotic process appears to have come to a standstill, and the vessels and nerves are encased by dense bands of fibrous tissue, sometimes of a hyalin nature.

If we examine a cross section of an artery or vein which is the seat of an old obliterative process, we often find an irregular, centrally placed lumen, a large amount of new formed tissue occluding the original lumen, and certain changes in the media; the whole picture giving the impression that there is an extensive proliferation of the intima, namely, an endarteritis obliterans. From a consideration of the descriptions which are to follow, we will understand, however, that the new masses in the lumen are not derivatives of the intima, but owe their origin to organization of obliterating red thrombi. In the occluding tissue we find a fairly large number of capillaries, some blood pigment, and fibrous tissue which is either rich in cells or has already become sclerotic in nature. Where the process is oldest, there the capillaries are few, the connective tissue has become dense, the pigment has disappeared, and either in the middle or near the periphery of the obliterating mass, there is a large dilated vessel



which is surrounded by connective tissue, and which simulates the remnant of the original lumen. In other vessels, there are large sinuses in the occluding mass, or dilated vessels separated by dense connective tissue; or there are atypical conformations in which two large blood spaces are separated by a septum that appears to spring from the intima of the vessel. The internal elastic lamina is thrown into marked folds and between it and the connective tissue described, there may be a slight or moderate amount of fibrotic change in the intermediate layer of Eberth. The striking lesion of the media is the presence of capillaries with or without a small amount of lymphoid infiltration in their immediate vicinity. Such capillaries may be present in small or in large numbers depending upon the age of the process; where the occlusion is recent, the signs of activity in the media are striking, the capillaries plentiful, the cellular infiltration marked. The fine vessels come in from the adventia, pass through the media, and penetrate the internal elastic lamina in order to vascularize the obturating mass.

What are the distinguishing features which enable us to differentiate an arteriosclerotic process from the lesions just described, and how can we establish the independence of the obturating masses from the intima, from which most authors would have them arise? By the employment of the elastic tissue stains, certain characteristics are brought to light which make it possible for us to say whether we are dealing with a thickening of the intima or with a new tissue lying in the lumen of the vessel. In arteriosclerosis we often find large obturating plaques which almost completely fill the vessel, the small space that is left being finally closed by a thrombus which becomes organized. It is not difficult to recognize such lesions as being arteriosclerotic when we note the large amount of elastic fibers in the plaque and note that these fibers are disposed for the most part parallel with the internal elastic lamina. In the occluding masses of so-called endarteritis obliterans, we find either a total absence of elastic fibers, or, when such are present, a growth of fibers around the larger canalizing vessels, particularly about those which are thick walled



and old. The differences in the two lesions are well elucidated by the pictures which we obtain when we examine vessels that show a combination of marked arteriosclerosis and so-called endarteritis obliterans. At times we find an occlusion of a vessel by obliterating masses at the site of an arteriosclerotic plaque, and then the distinctions which I have pointed out become very apparent. Some of the photographs which I pass around for your inspection show endarteritis obliterans. At times we find an occlusion of a vessel by obliterating tissue and intima, this will be better established when I have discussed the stages in the development of the process. Here I may simply mention the fact that the elastic tissue stains also show that it is only where a capillary penetrates the internal elastic lamina to vascularize the obliterating tissue, that there seems to be any direct connection between the two. The elastic fibers that belong to the thickened intima never pass over into this tissue except in those rare instances where the penetrating vessel has ruptured such fibers and has carried them for a short distance inward.

The most instructive histological pictures are those that are obtained in an examination of the vessels that are closed by transitional occluding tissue, and by this I mean obturation due to red thrombotic masses which can be traced into the softer brownish tissue and which finally may terminate in the dense old masses, the histology of which has already been discussed. In a number of cases, and especially well marked in the vessels in an extremity which was amputated because of pain without gangrene, such transitions from areas of red thrombosis into the older stages were found. If we examine a vein or artery at or near the termination of the red thrombus, we find a fairly recent clot filling the lumen of the vessel without change in the vessel wall. A short distance further the clot becomes adherent in places and the corresponding portions of the media show beginning lymphoid infiltration and the earliest signs of vascularization. At a point still further removed, the aspect of the thrombosis has considerably changed. A number of miliary foci, not unlike miliary tubercles, make their appearance near the periphery and there are

evidences of organization, such as the formation of capillary sprouts, fine capillaries and fibroblasts. The miliary foci present a central area of fibrin and one or more giant cells (probably phagocytic in nature) with cells not unlike endothelial cells in a peripheral zone. Such giant cell foci are but early stages in the process of organization. At another level the picture changes; the miliary foci gradually become lost; the vascularization of the clot becomes marked; the fibrin is almost absent; and numerous small round cells are scattered throughout. Here the media also shows quite a number of small capillaries with or without perivascular lymphoid infiltration. While the fine vessels in the thrombus at this level are thin walled, we soon note a change in their character. They become longitudinally disposed; here and there they connect with the media; they are surrounded by numerous round cells and fibroblasts and some blood pigment. These latter pictures correspond to the tissue which appears brownish and is not very firm. From this point on, the transition into the old type is fairly rapid. The cells in the obturating mass disappear and the fibrous intercellular substance becomes abundant; some of the capillaries atrophy; others become dilated, forming large spaces with well defined walls; at times there are numerous sinuses giving a fenestrated appearance; at times there is a centrally placed vessel resembling a much diminished lumen of the original vessel and sometimes such canalizing vessels are centrally placed. With this final maturation of the organizing process there are certain concomitant regressive changes in the media, namely, a diminution in the number of capillaries and the disappearance of alien cellular elements.

A detailed discussion of all the bizarre appearances that were found would take me too far, and I have therefore alluded only to those changes which seem to me to be valuable in clarifying the cause of the occlusion and which show that this is to be sought not in an endarteritis, but in the organization of red obliterating thrombi. I have described in brief the stages in the development of the process, and have shown how the old typical pictures can be directly traced into the areas of old and recent thrombosis,

and, further, how the changes in the media are dependent upon vascularization of the clot and are not primary. What other evidences have we to establish the correctness of our view of the process? A histological study of some of the terminations of the obturating tissue, particularly of the abrupt variety gives valuable information on this score. Thus if we make longitudinal sections through these rounded ends of occluding tissue which mark the cessation of the process in some of the vessels, we see how the closed portion of the vessel surrounds a vascular mass of young connective tissue and pigment; we note how the end of this mass rounds off, that it seems to be wholly independent of the intima except for points of junction by means of penetrating capillaries; and we are struck by the absence of pathological lesions just beyond the point of closure.

Finally, we must interpret the nature of those pictures which would at first sight be mistaken for obliteration due to proliferation of the intima; namely, those in which there is a large canalizing vessel more or less centrally placed, surrounded by a fair amount of elastic fibers. The paucity of elastic fibers in what would appear to be thickened intima, and the fact that the apparent remnant of the original lumen of the vessels usually divides at other levels into a number of smaller blood spaces, many of which finally communicate with the media, make it evident that we have here simply another product of the organizing thrombotic process.

Granted that we are dealing with a *thrombo-arteritis* and *thrombo-phlebitis obliterans* or *productiva*, how are we to explain the cause of the thrombosis? What role does the arteriosclerosis play in the lesion, and in what manner are the arteries and veins first affected? In view of the absence of completed studies on the nerves, the time is not ripe for any positive expression of opinion. We would at first hand be led to the belief that the changes in the intima are in great part responsible for the thrombosis. For this is doubtless the case in the secondary closure by clot in cases of senile and diabetic gangrene. Indeed, Zoege von Manteuffel takes the view that parietal white thrombi first lodge

in the popliteal and gradually extend downward; that they remain mural in nature, are of the white variety, and are rarely mixed with small red clots of recent origin. Practically every one of my cases furnished me with many evidences of the incorrectness of this conception. Thus the large territories filled with red thrombi with their transitions into the old occluding masses, the frequent absence of any change in the upper parts of the anterior tibial and posterior tibial when very distant parts were occluded, and, further, the presence of pulsation in the popliteal in some of the cases in which that vessel could not be examined: all these speak against his assumption. We gain the impression that the obturation ascends rather than descends; for the firmest and oldest tissue is most frequently found in the distal parts and not infrequently terminates in young thrombi or soft rounded abrupt terminations in the middle or lower part of the leg. Finally, the presence of the same lesion in the veins, which Zoege von Mantuffel had evidently not encountered, could certainly not be explained in the light of his theory.

Viewing the process from the standpoint of the pathological lesions, and considering certain facts obtained by clinical observation, it would seem most plausible to assume that certain territories, of either the arteries or the veins, become rather suddenly thrombosed, in a fashion similar to the thrombotic process which occurs in the superficial veins of the lower extremities. Thus at one time the dorsalis hallucis and dorsalis pedis, or perhaps the plantar arteries or veins, could become closed by red clot; and then the process of organization would take place. Perhaps after an interval of weeks or months, a similar process would cause extension upward, or affect other arteries and veins, until, after a lapse of many months, or a year, or more, practically all the larger vessels would become occluded. It is from a study of the age of the process in the various territories that we are led to this supposition. Here, too, as in the superficial thromboses, there is more tendency for the larger vessels to be involved than for the very fine ones; and, although the process seems to ascend, it probably does not originate in the capillaries or smallest



arterioles, but begins in branches of moderate size. The attendant periarteritis could be regarded as being either secondary or possibly as being produced by the same causes that lead to the thrombosis. Certain it is that the periarteritis is intimately linked with the presence of occluding masses.

In the future study of the etiology we ought to pay close attention to the rôle that syphilis may play in the production of these lesions. In none of the cases was it possible to obtain a definite syphilitic history, nor did they show any of the characteristic stigmata. Even the histological pictures leave us in doubt. Whatever may be the cause of the thrombosis, we feel inclined to take the view that, although the mechanical conditions that obtain in the lower extremities and the arteriosclerotic changes may be factors, some additional causative agent, be it toxic or otherwise, is at the same time responsible for the production of the periarteritis and of the thrombosis.

Taking the true nature of the lesions into consideration, I would suggest that the name "endarteritis obliterans" be no longer applied to the pathological changes under discussion, and that we adopt the terms *thrombo-arteritis* and *thrombo-phlebitis obliterans*, or, to be more concise, *thrombo-angecitis obliterans* or *productiva*.

I wish to express my indebtedness to Dr. F. S. Mandlebaum, Director of the Pathological Department of Mt. Sinai Hospital, for the preparation of the photomicrographs which I have shown to elucidate certain points in my paper. I wish to thank Drs. Lilienthal, Gerster and Sachs, for according to me the opportunity of studying their cases, and to acknowledge with pleasure the valuable assistance rendered me by Miss Adele Oppenheimer and Dr. Mark Cohn, volunteer assistants in the Pathological Department of Mt. Sinai Hospital.

#### *Discussion.*

DR. H. LILIENTHAL said that he could say nothing about the pathology of this extremely interesting condition. He thought that there was not much left to add; as far as accurate scientific



observation of cases goes, Dr. Buerger had pretty completely covered it, with the exception, as he had said, that study of the nerves might throw some light on the subject. Clinically, he might be able to add a word. These cases were seen at the Mt. Sinai Hospital in greater numbers probably than anywhere else in America. For this there must be some reason. Perhaps there was a poisoning of some sort; possibly due to eating rye bread which was ergotized. It was certain that in a person who had a tendency towards the disease, or had it in its incipency, the use of tobacco accelerated the course of the disease. Dr. Lilienthal spoke of the case of one man who had the disease of the arteries, who was in wretched general condition, and who finally had to have his leg amputated on account of gangrene. He had been an inveterate smoker and was advised to stop smoking entirely, which he did. A year after, his appearance was wonderfully changed. He reported that the pains which had begun in the other leg had practically disappeared, that the pain in the stump of the amputated leg had diminished, and that he was tremendously improved. This in spite of the fact that before amputation he had taken all sorts of drugs in the hope of warding off the trouble. It was an interesting clinical fact also that in spite of the obliteration of the arteries the bones of these patients heal very nicely. In a number of cases Dr. Lilienthal had performed osteoplastic operations, covering the bone marrow with a little piece of bone which remained attached by periosteum as by a hinge (Bier's method). The method had been found to work perfectly well. Even in a leg in which there had been gangrene one could perform the osteoplastic operation; the circulation in the bone seemed to be good enough to give perfect union. A man at present under observation had been operated upon in this manner, and in spite of the fact that there was a little spot of necrosis of the bone there had been no breaking down. Dr. Lilienthal felt sure from past experience that the wound would eventually heal entirely. One would think that in so ill-nourished a tissue as a little piece of bone attached only by a flap of periosteum, if the arteries were all diseased, union would not take

place. He thought there must be some difference in the arteries in the bone, and asked Dr. Buerger if he had decalcified the bone and examined the arteries. A sad part of these cases was their occurrence in young people; he had had patients as young as twenty.

DR. T. C. JANEWAY asked Dr. Buerger whether he had made any observation on the relation of the venous thrombosis to the clinical type with cyanosis. Did that represent a later stage of the process?

DR. I. LEVIN congratulated Dr. Buerger on the thoroughness of his study. From the standpoint of pathology, he thought it the most thorough study which had been made on the subject. Dr. Buerger's conclusions seemed at first to be entirely original. There were a number of different theories held in regard to this condition. There is a school that considers proliferation of the intima as the primary cause. There is a school that considers that while the primary condition is a disease of the intima, still the thrombus formation is the real cause of the gangrene. Some writers consider the media as the primary cause of the disease, and Dr. Levin had somewhat come to the same conclusion. Dr. Buerger seemed to consider that the primary condition was the formation of the thrombus, but Dr. Levin did not understand how he explained the formation of a thrombus in a healthy vessel with healthy walls. The understanding in pathology was that thrombosis would occur only through embolism, or else through a diseased wall of the vessel. At the end, Dr. Buerger had said that he thought some kind of intoxication or disease of the intima must have occurred before the thrombosis took place. If that were so, the difference between his opinion and that of others would not be so great. It seemed to him that we could not very easily exclude any part of the wall of the vessel in that diseased condition. There was most probably a disease of the whole vessel wall, whether it were most marked in the intima or in the adventitia. It seemed to him that while in the majority of Dr. Buerger's cases the most important factor had been the thrombus formation, one photograph which he had explained as thrombus

with canalization in the center, looked more like real proliferation of the intima without any thrombus. The canal of the blood vessel instead of having a circular form showed a rather narrow broken formation. As regarded the clinical side of the question, Dr. Levin wished to say a word about the rye bread which Dr. Lilienthal had mentioned. The works on this subject showed that the disease usually occurred in Russian Jews, and not in Russian Gentiles; the Russian Gentiles, however, eat only rye bread.

DR. B. LAPOWSKI asked whether, when Dr. Buerger spoke of a fresh thrombus forming independent of the vessel, he meant that the vessel wall at that point was not changed. If the intima was changed, there was no difference between his and Zoege von Manteuffel's opinions. The formation of the primary thrombus in such cases may be due to the changes. Dr. Buerger spoke of an acute formation of thrombus in the wall; but this would not answer to the clinical picture. Usually the clinical picture lasted for years. Dr. Lapowski said that cases of the disease had been reported in Russian Gentiles. The disease had been ascribed to severe cold. Probably 98 per cent. of the cases reported were among Russian Jews, but this was because the doctors (Goldflam, Higier, Idelsohn, Erb) who describe the cases have a practice among those people. As regarded syphilis, Dr. Lapowski did not agree with the opinions expressed. He had seen several cases which had responded to mercury though there had been no direct manifestations of syphilis. He thought every case should be treated for syphilis and then carefully watched. If there was any improvement, the treatment should be continued, for years if necessary, before amputation. One of the cases mentioned was under the speaker's care, and was improving under syphilitic treatment; the gangrene of the fingers had entirely disappeared, the fingers assuming their normal aspect; and the ulcers on the toes were also improving, though more slowly. If the treatment had had a longer trial the former amputation would have been unnecessary.

DR. J. H. LARKIN hoped that even the thorough work which

Dr. Buerger had done would not be accepted as final. Not long ago Dr. Levin had presented a case which had aroused a great deal of discussion. Thorough dissection of that leg showed conditions which were at great variance with the conclusions given by Dr. Buerger. He did not think very much of the photographs as proving the points. He did not think that as regarded the pictures one could at all leave out the connection of the intima and thrombus formation. In Dr. Levin's case there had been a great amount of endarteritis; the musculature also played a very important part. Dr. Buerger's remarks about organization of the thrombus as derived from proliferation of the connective tissue from the media, leaving out the intima, seemed to touch on a very difficult point.

DR. A. V. MOSCHCOWITZ thought that Dr. Buerger, Dr. Levin, and Dr. Larkin might all be right. In the various cases of gangrene there might be different findings. Clinically the cases differed very much. Some patients feel pain when the leg is in the pendent position; others when the leg is elevated. Some cases present marked pain when the foot is cyanotic; others when it is pale. It seemed to him that these points could be very well brought together. Moszkovitz, of Vienna, had brought up the question where to operate. The speaker had tried the method, which might be of interest to the Society. An ordinary Esmarch bandage was applied and the leg was elevated. After the elastic bandage had been on for three or four minutes it was taken off. When the hyperemia returned it usually showed a sharp edge; that was the place where the amputation should be done. Amputation above that line was usually unnecessarily high. If the amputation was done below that line there was apt to be secondary gangrene of the stump.

DR. E. LIBMAN thought that it was a cause for congratulation that a subject had been found which was of interest to the clinicians as well as to the pathologists. On looking over the constitution recently he had found that the objects of the Society were stated as "the advancement of the knowledge of pathological anatomy, histology, and general pathology, and the improve-



ment of its members in these departments, and in the diagnosis and treatment of disease as founded upon them." He thought that it would be wise to have clinicians and surgeons interested in the work of the Society.

DR. BUEGER said, in answer to Dr. Lilienthal's question as to whether he had examined the vessels in the bones, that he had not included these in his study because he did not think that the small vessels would be affected by the obliterating process, inasmuch as they usually showed only a moderate degree of arteriosclerosis elsewhere. He thought that a number of gentlemen who had discussed his paper had failed to see that he wished particularly to bring out the fact that the lesion in the vessels was one due to thrombosis and not to endarteritis. Hence Dr. Levin's statement that the views of other authors were not so very different from the one suggested by him. He could readily see how Dr. Levin could be mistaken in the interpretation of certain of the photographs presented, for the picture produced by an obturating process arising from the intima, and that produced by canalization of a thrombus, may be so similar that only the elastic tissue stains and the study of the future course of the central canalizing vessel would clear up the nature of the process. In reference to Dr. Larkin's remarks, Dr. Buerger pointed out that the slides which he exhibited showed much better than the photographs the various stages in the development of the process. Dr. Janeway had asked whether there was any relation between the pathological findings and the clinical symptoms, as far as the ischemia and cyanosis were concerned. Dr. Buerger remembered one case in particular, in which there was marked involvement of the veins and in which the erythromelalgic and cyanotic symptoms were very pronounced. Many of the superficial veins were thrombosed in a manner similar to the deep vessels. Possibly the cyanosis is of greater degree whenever the veins are markedly diseased. The case which Dr. Lapowski had described, had been carefully observed by the speaker for about four years. In this patient the disease commenced in the upper extremities as a migrating phlebitis extending in quick succession upwards



through the superficial veins of the forearm. About four years ago a piece of one of the thrombosed veins was removed at Mt. Sinai Hospital, and Dr. Mandlebaum, the pathologist, reported the lesion as being an obliterative thrombo-phlebitis, possibly syphilitic in nature. Curiously enough, this patient developed the typical symptoms in both lower extremities, the erythromelalgic signs, coldness, pain, and trophic disturbance. In addition, however, he had frequent attacks during which the superficial veins of the lower extremities became thrombosed. It was more than probable that the deep vessels of the leg were affected by a process similar to that which had first appeared in the upper extremities.

In analyzing the literature, Dr. Buerger said, we must not become confused by statements regarding thrombosis in the arteries in cases of gangrene. Careful investigation of the findings of most authors reveals the fact that many of the important instances of thrombosis occurred in patients suffering from marked arteriosclerosis in which a secondary thrombosis had taken place. Dr. Buerger did not wish to convey the impression that all cases of spontaneous gangrene of the lower extremities in young people were due to the same cause, or were of the nature he had described, and he therefore did not question that the media was the seat of disease in Dr. Larkin's case. Finally, he said, we should not place too much reliance upon the Moszkovitz test because it demonstrated the patency of collaterals rather than of the original vessels, and it must be remembered that the collateral could at any time become closed and the nourishment of the part could suddenly become impaired.

---

# Proceedings

of the

## New York Pathological Society.

---

New Series, Vol. VIII.

APRIL and MAY, 1908

Nos. 3 and 4

---

### TABLE OF CONTENTS

SATTERLEE AND SABEL, Colon Irrigations in the Treatment of Pernicious Anemia.—WOOD, A Case of Primary Carcinoma of the Liver.—ZINNser, Notes on Arteriosclerosis of the Pulmonary Arteries; A Case of Typhoid Bacilli in the Gall-Bladder.—OPPENHEIMER, Radial Fibres in Arteries (Duerck).—EWING, Myxoma and Diffuse Hyperplasia of a Full Term Placenta; An Intrauterine Perithelioma.—Moschcowitz, Typhoid Fever with Mixed Infection.—MANDLEBAUM AND CELLER, Lesions in a Case of Myasthenia Gravis.—STRAUSS, Two Atypical Kidney Tumors.—FIELD, Agglutinating Action of Ricin on Erythrocytes in Isotonic Sugar Solution.—JOBling, A Report on Mouse Tumors.—HEss, A Case of Tuberculosis in a Cat.—CROHN, Blood Cultures in Glanders.

---

DR. E. LIBMAN, *President.*

---

### COLON IRRIGATIONS IN THE TREATMENT OF PERNICIOUS ANEMIA.

G. R. SATTERLEE, M. D., AND S. O. SABEL, M. D.

Dr. G. R. Satterlee reported for himself and Dr. Sabel two cases of pernicious anemia which had been treated with colon irrigations.

The first case was that of a male, forty-four years of age, who entered the Washington Heights Hospital on October 16, 1907, suffering from indigestion, palpitation and dyspnea. There was

no history of syphilis or gonorrhea; the patient drank in moderation. He had not been ill up to two years before. He then had had bronchitis for four months, which had been treated without relief. This was followed by intestinal troubles and severe diarrhea. He lost weight and noticed a peculiar greenish color of the skin. He had spots before his eyes and for one and a half months was totally blind; he also had palpitation of the heart. Under treatment he improved up to three months before admission when the symptoms returned.

Physical examination showed a picture characteristic of severe anemia of pernicious type. The mucous membranes pale, sclera pale, pupils normal. There were evidences of stomatitis and glossitis, and the edges of the tongue were raw. No glands were palpable except in the inguinal region. The spleen was just palpable. Blood examination showed red cells 2,980,000, leucocytes 12,000, polynuclears 51%, lymphocytes 49%; no eosinophiles. Blood smears showed megaloblasts, microcytes, and marked poikilocytosis. The patient was put on a bread and milk diet with administration of egg albumin and ferric chloride. The chief symptoms while in the hospital were vomiting, diarrhea, and offensive odor to the stools; no parasites were found. Sputum contained no tubercle bacilli. The urine was of a specific gravity of 1.020 to 1.025, and contained a trace of indican. The patient's condition grew worse and he complained of disagreement of medicine, so that all drugs were stopped. Colon irrigations were begun on October 3, normal saline solution being used. The stools were very foul and contained blood and undigested food. Marked improvement was at once noticed and in four days the patient was out of bed. Gastro-intestinal symptoms continued. The only treatment from this time on was colon irrigation. Blood examination showed gradual increase of red cells and percentage of hemoglobin and polynuclear leucocytes. During the last week of his life the patient grew worse and had a severe cough. Temperature during the course of his illness was above normal, for

part of the time 102° or higher. Just before death he had an hemoptysis. Autopsy showed hydrothorax, hypostatic pneumonia, hyperplasia of lymphoid follicles, dilatation of the heart, right side, atrophy of the bone marrow of the ribs and vertebrae, dilatation of the stomach with a double stenosis, giving a triple sacculated appearance to the organ as seen in the specimen presented. Microscopically the mucosa showed an infiltration around the glands of round cells and fibrous tissue. The spleen was enlarged two and one-half times. There was chronic interstitial hepatitis, chronic interstitial pancreatitis, chronic parenchymatous nephritis. Both large and small intestines were congested; no parasites or ova could be found; no ulcerations. Microscopical examination of the bone marrow from the femur showed a large number of nucleated red cells, diminished proportions of bone marrow cells, no eosinophiles or fat cells.

The second case was that of a woman, fifty-five years of age, admitted to the Washington Heights Hospital, June 21, 1907. The patient's history showed a long period of constipation with much gastric trouble. No bad habits, no syphilis. The patient complained of chills, weakness, vomiting and constipation. Physical examination showed pronounced anemia. Blood count gave red cells 1,940,000, hemoglobin 26%, leucocytes 6,200. There was a large proportion of megalocytes with few microcytes and polynuclears. No nucleated red cells appeared at first. Special features were flatulence, vomiting now and then, extreme weakness and constipation. There were a few hyalin casts and red blood cells in the urine. There was marked brownish pigmentation of the skin and general desquamation. Colon irrigations were begun July 23 and were continued until two weeks before the patient left hospital with marked improvement; hemoglobin quickly rose to 50%; red cells increased; nucleated reds disappeared.

CONCLUSIONS:—The predominating symptoms in these cases were not only those of severe anemia of pernicious type, but also

of severe gastro-intestinal troubles. Both cases started with intestinal disturbances. During the colon irrigations the symptoms and general conditions were improved; but in case 1 they were begun too late to be of avail. In the second case the symptoms were markedly improved. If the disease is due to an intoxication colon irrigations would seem to be a rational way of treating, if not of curing, it; but if begun too late would be, of course, of doubtful efficiency.

Hunter had concluded that pernicious anemia is a specific condition resulting from excessive hemolysis; in 1907 he stated that it was an infective disease localized in the intestine. The gastric lesions were considered by Hunter as the seat, not only of the primary infection, but also of its development. Herter has shown that the presence of certain forms of bacteria breaks down proteids suitable for the use of other putrefactive organs, and that putrefaction is responsible for indican.

Drs. Hollis and Ditman have reported two cases of pernicious anemia treated by colon irrigations with very marked improvement. Dr. Hollis had since stated that the first case had died because of drink, and the second case had a relapse through overwork and was again under treatment.

The two cases of Dr. Satterlee's were reported in the hope that they might be of help in determining the etiology and mode of treatment of this disease.

### *Discussion.*

DR. F. C. WOOD said that he had followed the cases reported by Drs. Hollis and Ditman, and at the time of their report had called their attention to the fact that the blood still showed the type of pernicious anemia. The cases were merely in the stage of marked remission. One case had already died, and the other case was now in St. Luke's Hospital and was practically moribund. Dr. Wood had seen two other cases, one a woman followed



for three years, who had been faithfully treated with colon irrigations and who showed only slight improvement for short periods, and finally died. She had never done any work and had taken good care of herself. The other case was that of a business man on whom the irrigations had produced not the slightest effect. While the blood examinations showed great variations the changes were not at all connected with the colon irrigations, which he had kept up regularly. Dr. Wood thought the improvement seen in many of the cases might be due entirely to the increased peristalsis and improved nutrition, and not necessarily to the removing from the bowel of hemolytic toxic substances.

DR. JAMES EWING said that recently Dr. Schaffer had examined for him the stools of a prolonged case of pernicious anemia, two days before death, when the hemoglobin was about 8%. He was unable to determine any increase in the ordinary putrefactive products of the intestine, as indol, skatol, and phenol.

DR. SATTERLEE said in regard to Dr. Wood's cases that of course, where one got pernicious anemia late in the disease the colon irrigations were hopeless. It was only in the beginning of the disease that they might have some effect.

## A CASE OF PRIMARY CARCINOMA OF THE LIVER.

F. C. WOOD, M. D.

Dr. F. C. Wood presented specimens from a case of primary carcinoma of the liver which showed very well the gross lesions of the condition. The specimen was removed from a case dying at the German Hospital. An exploratory laparotomy had been done on the patient who was supposed to have either gall-stones or a secondary carcinoma. The symptoms were jaundice and a large liver, together with failing strength. A small piece of the

liver was excised at the time of operation and the diagnosis was made. The patient died about a week after the operation. Dr. Wood had seen only three of these cases of primary carcinoma of the liver in his experience, all showing about the same type of tumor. Sections of the nodule showed a tumor which varied a great deal. Some portions were adenomatous; others differed considerably from the normal liver cell and might be properly considered as carcinoma. There were, of course, degenerative and other changes in the liver cells which were often of large size. The diagnosis of adenocarcinoma was suggested. There were many mitoses in the tumor tissues. There were no metastases found, metastases being rare in this type of tumor. Under the microscope the sections showed fatty changes in the tumor cells and other cells of the liver. It was striking that there was practically no cirrhosis of the liver, and also that the liver cells were of enormous size, two or three times the size of normal liver cells.

The case will be published in full later.

---

## NOTES ON ARTERIOSCLEROSIS OF THE PULMONARY ARTERIES.

HANS ZINSSER, M. D.

Although the occurrence of vascular disease in the pulmonary circulation is by no means a rare phenomenon, there are many factors in its relation to similar disease in the systemic circulation, which have seemed to justify the presentation of the subject to this Society.

Since 1850 and the years following, when the condition was first described by Dittrich and Bamberger, the number of cases of the lesion reported has rapidly multiplied, the various authors agreeing with more or less emphasis that arteriosclerosis in the

smaller circulation is in some way related to the increased intravascular pressure accompanying cardiac disease, especially disease of the mitral valve. The frequency of the disease, however, has been, even to the present day, a matter of controversy, von Schrötter, as recently as 1899, claiming that the lesion was of comparatively rare occurrence. Brüning, who carefully studied a series of twenty-one cases, reached the conclusion that the lesion is much more frequent than is generally supposed, and that even in cases where no macroscopic disease is demonstrable, microscopic examination may reveal lesions in the smaller vessels.

The questions which arise with particular insistence in the study of this lesion are, first, in how far do these changes in the pulmonary vessels depend upon the local influence of intravascular pressure due to cardiac disease? and, second, how closely is the lesion dependent upon co-existent disease in the systemic circulation?

In the course of the past few months the writer has had occasion to note the occurrence of pulmonary artery atheroma in fifteen cases, which may be briefly summarized. A large number of these were placed at the disposal of the writer by Professor Hodenpyl of the College of Physicians and Surgeons.

Of these, nine were cases of mitral stenosis, six of marked, three of moderate degree.

Five of these cases showed extensive lesions of the circumscribed variety of atheroma, patches extending into the very smallest branches that could be macroscopically examined. Microscopic examination of these cases, by the Sudan III frozen section method, showed fatty degeneration apparently beginning in the media, in other vessels involving the subendothelial layers of the intima. The changes noted consisted chiefly in thickening of the coat involved by a proliferation of delicate connective tissue in which the nuclei were abundant and the fibrils delicate and apparently loosely arranged. In all of the lesions, fatty degeneration of marked degree was present. Calcification was never noted.

Accompanying the fatty degeneration, there was usually seen young proliferating connective tissue with thickening of the vascular walls.

Other specimens, run through by the usual histological methods, showed no demonstrable lesions in the very small branches. In but one of these cases were similar patches noticed in the pulmonary veins.

The other four cases of mitral stenosis showed macroscopic lesions of only moderate degree, but still extending into the tertiary and further bifurcations of the pulmonary arteries.

Eight of the nine cases showed aortic atheroma; but in all but two of these the aortic lesion was insignificant, and in no way comparable in severity to the lesion in the pulmonary vessels. Two of the cases showed thrombi in the pulmonary vessels with infarction.

Of the remaining six cases, four were cases of chronic nephritis with marked aortic atheroma; two were cases of old subjects with myocarditis and cardiac dilatation. It was noteworthy that one of the nephritis cases showed the most extreme degree of aortic ulcerative lesions with but slight changes in the larger branches of the pulmonary vessels.

Through the courtesy of Dr. Hodenpyl, two other cases of unusually severe aortic lesions were examined, neither of which showed any lesion in the pulmonary circulation. As much of the material from which these data were taken came from the Morgue, little information as to previous history could be obtained, and the question of syphilis, rheumatism, etc., can not therefore be considered. Of four cases which came from St. Luke's Hospital, and of one which was kindly given to the writer by Professor Wood from the German Hospital, histories were obtainable. Only one of these, one of the mitral stenosis cases, gave an unquestionable history of syphilis.

To sum up the observations in these cases, then, all the mitral stenosis cases examined have shown the lesion of the pulmonary

vessels to a more or less extreme degree. In none of the cases was there any relation between the severity of the lesions in the aorta and in the pulmonary vessels. In none of the cases in which there was no cardiac disease with consequent increased intravascular pressure was the lesion at all extensive. None of these observations, the writer is aware, are particularly new; but they support in the main the statement of other writers.

Histologically, the conditions found correspond with those observed in similar cases by Thorhorst, Brüning, and others, differing only from the observations of the last named author, who found the smaller branches often diseased when no macroscopic lesions existed in the larger trunks.

The cases studied, as a whole, bear out the close relation of the lesion to mitral stenosis and the consequent pulmonary congestion, and the independence of the pulmonary vascular disease from the condition of the systemic vessels. This fact has been a source of much theorizing. Von Schrötter after studying the pulmonary and systemic arteries carefully found no histological differences in vessel structure to account for it. Rosenbach attributed it to the pulmonary circulation obtained from the respiratory movements of the chest, which facilitated the circulation through this system. The reason for the independence of the lesions in the two circulatory systems from each other is made clear by the work of Tigerstedt, Gerhardt, etc., who have shown that in order to increase appreciably the pressure in the pulmonary circulation, the systemic pressure must be raised to almost double the normal.

Two cases observed at St. Luke's Hospital, however, are of special interest. Both of these cases—old mitral stenoses—were accompanied by pulmonary thrombi with infarction. In neither of them could thrombosis in other vessels be found, nor had it been clinically suspected. In one of them there were recent vegetations upon the tricuspid valves. Cultures from the pulmonary thrombus in one of these cases showed *Bacillus coli* (the autopsy



was not done until six to eight hours after death); in the other case, cultivation was unfortunately omitted. In the absence of traceable source for embolism, without sepsis, and with marked arteriosclerotic changes in the pulmonary vessels, together with marked chronic congestion, it did not seem unreasonable to consider the possibility of a predisposition to pulmonary thrombosis brought about by the marked disease of the intima of the blood vessels.

### *Discussion.*

DR. E. LIBMAN said that he thought the question was one of great interest. He had been making notes on these cases for some years, and had for a long time been looking for a case like the one described by Romberg of extensive atheroma of the pulmonary vessels. The clinical diagnosis in this case was congenital cardiac disease, and the patient had arteriosclerosis of the pulmonary vessels only.

---

## A CASE OF TYPHOID BACILLI IN THE GALL-BLADDER.

HANS ZINSSER, M. D.

S. P., married, forty years old, admitted February 10, 1907. *Past history*: measles, scarlatina, pertussis, as a child. *Personal history* (procured later by the House Physician): illness sixteen years ago, probably typhoid. Three years ago some obscure gastric trouble lasting two months. Chronic constipation. Two months before admission, the patient began to feel run down, and lost her appetite; constipation increased; and she complained of pains in the abdomen. She did not at this time vomit, but was frequently nauseated. This continued until one or two weeks

before admission, when she noticed jaundice which since then has been steadily deepening. At the same time there was tenderness over the gall-bladder region and over the appendix. The edge of the liver could be felt and was tender. The stools were light in color, the urine dark. On admission, her temperature ranged from  $101^{\circ}$  in the afternoon to  $98^{\circ}$  in the morning, for about four days; it then quickly ascended until on the afternoon of the seventh day it reached  $104^{\circ}$ . The blood count showed 8,400 leucocytes, 74% of which were polynuclears. No bile was found in the stools, but there was a great deal in the urine.

On February 21, the patient was operated upon. The gall-bladder was found to be distended with pus, and a gall-stone, the size of a hickory nut was removed from the gall-bladder.

*Synopsis of Autopsy Protocol*:—The body was deeply jaundiced. Heart normal; pericardium contained bile stained exudate. The lungs were congested and edematous. The gall-bladder was dilated with a large quantity of bile and blood, and measured 8x6 cm. There was marked dilatation of hepatic and cystic ducts. The common duct was normal in size. Just beyond the entrance of the cystic duct into the common duct, there was a stricture, apparently old, containing small concretions. Next to the strictured portion of the duct there was a hard mass, the size of a hickory nut, which looked like an enlarged gland. At autopsy the stricture was thought to be benign, but section of this portion of the duct revealed carcinoma.

*Bacteriological Findings*:—In the pus in the gall-bladder, a bacillus was found in pure culture which later turned out to be a typical *Bacillus typhosus*. In smears from the pus and in the first transplants from this pus, the bacillus appeared extremely short, fragmental, and coccoid, the morphology being more like that of one of the members of the colon group than like that of *Bacillus typhosus*. The motility was very slight, though distinct, very much less than in the average typhoid culture as observed in the laboratory.

The interesting point in the study of this bacillus was the fact that, it being probable that the bacillus had dwelt in the human body for sixteen years, there were practically no important cultural changes in the micro-organism. Its sugar fermentations were entirely unchanged, in that fermentation took place with acid formation in dextrose, levulose, galactose, mannit, maltosë (late), and dextrin; but not in lactose and saccharose. Gas was not formed on dextrose, on lactose, or on saccharose. Gelatin was not fluidified. The only atypical cultural reaction was that in the Hiss tube medium, where the very slight motility of the bacillus resulted, in early cultures, in close adherence to the stab, instead of general clouding. This, however, soon changed, the third, fourth, and subsequent transplants showing almost equal motility to the stock cultures. The agglutination reactions of this bacillus showed several points of interest. With the patient's blood this bacillus agglutinated in dilutions up to 1-300; whereas the patient's blood agglutinated a stock typhoid culture used for Widal reactions only 1-40. Agglutinated against typhoid immune serum and controlled by three laboratory strains of *Bacillus typhosus*, the bacillus from the patient agglutinated as highly as the others, the dilutions being carried to 1-1000.

It is not by any means clear exactly what this means. It seems to indicate that the blood of the patient had retained the specific agglutinin for this bacillus, but had, in the course of time, lost the group agglutinins for typhoid bacilli in general. This bacillus, on the other hand, had not lost those agglutinogens which rendered it subject to agglutination by a general typhoid immune serum.

#### *Discussion.*

DR. L. BUERGER asked whether the stools in this case had been examined for typhoid bacilli.

DR. ZINSSER said that they had not been examined, but that at the time of autopsy he had removed specimens from different

parts of the intestine from which cultures were made. In but nine was he able to find typhoid bacilli. He thought that the bacilli were probably there but were not demonstrated.

DR. C. W. FIELD asked whether any absorption experiments had been done with the organism. It might not agglutinate either microscopically or macroscopically, and still absorb from the serum the specific agglutinins, though not showing any agglutinating action.

DR. ZINSSER said that he had not made such experiments.

DR. JAMES EWING asked Dr. Zinsser whether he had tested the agglutinating effect of this patient's serum on any form of colon bacillus, especially on any colon which might have been found in the patient's intestine.

DR. ZINSSER said that he had not.

DR. E. LIBMAN asked whether the stricture of which Dr. Zinsser had spoken was complete. If it were, it might perhaps explain the absence of typhoid bacilli from the stools.

DR. ZINSSER said that the stricture was made complete by the small concretions in the duct which were pushed away by the probe.

---

## RADIAL FIBRES IN ARTERIES (DUERCK).

ADELE OPPENHEIMER.

In *Virchow's Archiv* for July, 1907, Duerck reported that by means of Weigert's recent myelin-sheath stain he was able to demonstrate elastic fibres with exquisite distinctness and to show clearly that the elastic tissue system of arteries is not exactly what we have heretofore supposed it to be.

Recently Dr. A. E. Cohn sent Dr. Libman sections of arteries stained by means of Weigert's earlier myelin-sheath stain, which

aroused our interest. These were prepared in Professor Aschoff's laboratory.

There are under two of the microscopes to-night, cross sections of arteries stained (1) by Duerck's method and (2) by Dr. Cohn's method, that is with Weigert's earlier and later myelin-sheath stains.

Duerck's method as we have employed it is as follows:

1. Fix in Orth's formol-Mueller 24 to 72 hours.
2. Do not wash.
3. Imbed in paraffin or celloidin and cut thin sections.
4. Mordant with Weigert's neuroglia mordant for 24 hours.

This mordant consists of:

Chrome alum 2.5 parts.  
Water 100.0.  
Acetic acid (36%) 5.0.  
Neutral copper acetate 5.0.

5. Wash briefly in 70% alcohol.

6. Stain with Weigert's iron hematoxylin stain which consists of solutions A and B, equal parts, mixed just before use:

A is 1% hematoxylin in 95% alcohol.

B consists of:

Ferric chloride fortis 4 c.c.  
Hydrochloric acid 1 c.c.  
Water up to 100 c.c.

7. After staining over night, wash in distilled water.
8. Differentiate in the following solution:

Potassium ferricyanide 2 parts	} Diluted with three parts of water.
Borax 2.5 parts	
Water 100 parts	

9. Wash in tap water, thoroughly.

10. Pass through three grades of alcohol, and through xylol, and mount in balsam.



Weigert's earlier myelin-sheath stain is very similar to this later one—it is also a cupric acetate-hematoxylin method, but simpler.

After treatment of sections according to these cupric acetate-hematoxylin methods, the elastic fibres stand out as if drawn with blue black ink on a tan background.

The sections stained according to the simpler method show in contradistinction to slides stained with orcein or with fuchsin-resorcin (1) many more fibres and (2) a well marked network. It is an open question whether this network is elastic or not.

The sections stained according to Duerck's method present an appearance very similar to those stained with orcein or fuchsin-resorcin.

In cross sections of medium sized and larger arteries, Duerck points out that there are seen in addition to the elastic elements between the muscle fibres, *many radial elements* stretching between these well-known circularly arranged elastic fibrils of the tunica media and binding them together. By means of these innumerable radial fibres, the elastica interna, the elastica externa, and the intermuscular elastic fibres of the mesial coat, and even the elastic elements of the adventitia of the arteries become one whole, are bound into one system.

Duerck is of the opinion that these elastic radial fibres dilate the vessels automatically. He suggests that the vessels are contracted after nerve stimulation of their circular muscles, then dilated automatically by the radial elastic fibres.

---

## MYXOMA AND DIFFUSE HYPERPLASIA OF A FULL TERM PLACENTA.

JAMES EWING, M. D.

The specimen, for which I am indebted to Dr. W. M. Polk, was obtained from a patient who was delivered of a well formed infant at about term. The child lived only a few minutes. The pregnancy was uneventful, but unusual enlargement of the uterus had suggested the existence of twins. The placenta was delivered with some difficulty on account of its size. The organ measured 25 x 22 x 4 cm. There was a typical battledore insertion of the cord. Projecting from the fetal surface near the insertion of the cord was a rounded, firm, congested tumor, 16 x 8 x 4 cm. The lobules of the placenta throughout were very large, and the tissue was opaque, firm, light colored, and free from infarcts.

On section, the isolated tumor was composed of broad areas of myxomatous tissue interspersed with very numerous small villi. The spaces between the original villi were obliterated or compressed into narrow slits lined with flattened cells. The reddish color of the isolated tumor was due to retention of a moderate amount of blood in these narrow spaces. The cells of the myxomatous tissue were not very much increased in number except in certain foci, and the increase in bulk of the tissue was largely referable to increase of mucoid stroma. I was unable positively to identify mitotic figures. Throughout the remaining portions of the placenta, which was much increased in bulk, there was a pronounced increase in cells in and on the villi. Langhans' cells and syncytium were poorly differentiated, and the basement membrane separating Langhans' cells from the stroma of the villi was very faint or apparently absent. There was thus a diffuse hyperplasia of all stroma cells and lining epithelial cells of the villi throughout the placenta and this condition was responsible for the firm, opaque gross characters of the organ. The

exact significance of this change and its relation to the more definite localized myxoma, I am unable to explain.

The umbilical cord was of small diameter, and after hardening in formalin was of almost cartilaginous density. The vessels were tortuous. On section, no changes were found in the vessels of the cord, but the mucoid connective tissue contained an unusual admixture of collagenous fibrils, instead of the mucoid stroma.

Von Winckel states that about fifty tumors of the placenta of this general type are recorded. None of them proved malignant.

---

## AN INTRAUTERINE PERITHELIOMA.

JAMES EWING, M. D.

This specimen, for which I am indebted to Dr. John Rogers, shows a very unusual structure among uterine tumors, and its exact nature I am unable to determine.

The patient, married, forty-eight years of age, had not menstruated since December, 1904 (three and one-half years). No history of abortion could be obtained. In January, 1908, irregular bleeding from the uterus began, sometimes profuse, with intervals of remission lasting a week. In March, a foul discharge began, and continued steadily, accompanied by frequent bleeding.

On admission to the hospital, the uterus was found enlarged, and tender; the os was patulous, discharging muco-pus; and a large tumor distended the cavity. The condition was regarded as a probable suppurating fibroid, while the suspicion of a malignant tumor was suggested by the spongy character of the mass. Hysterectomy was therefore performed, and was followed by prompt recovery.

*Gross Examination.*—The uterus measures 77x7 cm. On incision the uterine cavity was found to be occupied by a rounded, polypoid, solid tumor, measuring 10x6 cm., firmly ad-

herent over the anterior wall and projecting into and distending the cavity. The tumor was rather fragile, and on section was streaked with extensive areas of necrotic tissue. The uterine wall was thinned especially over the attachment of the tumor, and here the tumor edge was irregular, some nodules lying slightly within the muscularis; and along this portion necrotic areas were missing.

*Microscopical Examination.*—Fixation in 10 per cent. formalin. The outer half of the tumor was composed about equally of necrotic structureless material and masses of large polyhedral cells in advanced granular and hydropic degeneration. The deeper portions of the tumor are better nourished, supplied with a few delicate blood vessels, showing only occasional miliary foci of necrosis and composed of polyhedral cells in close apposition. These cells have well defined borders, clear or granular protoplasm and vesicular nuclei. In size they vary from 15 to 30 micra. Near the blood vessels the smaller cells predominate. Mitotic figures with well preserved spindles are very numerous, especially in the deeper portions near the muscularis. The growth of cells is nearly diffuse, no sinuses and no villi being found.

While a histological diagnosis of perithelioma is easily reached for this growth, yet the origin of the tumor is not clear. Three possibilities may be suggested. It is possible that the tumor arose from the stroma of the uterine mucosa, but I am not aware that any such tumors have been shown to take origin from such tissue. I was at first inclined to consider the possibility that the tumor was a true deciduoma; but no such growths have been observed from placental remnants, villi could not be traced in the tumor tissue, and the clinical history was against a recent pregnancy. Finally, it is possible that the tumor arose from an adrenal remnant, either primary in the uterus, or as a secondary growth after a primary tumor elsewhere of which no clinical signs were obtainable. The structure is distinctly that of hypernephroma. The future history of the patient may perhaps determine this point.

## TYPHOID FEVER WITH MIXED INFECTION.

E. MOSCHCOWITZ, M. D.

Dr. E. Moschcowitz described a case of typhoid fever in which there had been a mixed infection with the *Streptococcus pyogenes*. The case was of interest for two reasons; first, because of the rare association of the typhoid bacillus and the streptococcus; and, second, because the pathological findings were not those ordinarily found in typhoid fever. The patient was a woman, fifty-two years of age, whose previous history was entirely negative. She first became ill on September 27, 1907. The symptoms complained of were intense headache, generalized pains, chilly feelings, and a slight fever. The temperature was  $103^{\circ}$ , pulse 110. Physical examination was entirely negative, with the exception of a few dry râles at the right base, which cleared up within a few days. The diagnosis of influenza was made, but despite the administration of appropriate remedies the temperature continued high. The Widal reaction was negative, and although taken every other day during the course of the next two weeks, remained negative. The temperature was of a very irregular type, and the pulse varied between 110 and 120; physical examination was still entirely negative. Nineteen days after she first became ill, a blood culture was taken and the report was "typhoid bacilli and streptococci." There were never any rose spots; the spleen was never palpable; or was there abdominal tenderness or distention. Antistreptococcus serum was injected twice, a few days apart, without any effect on the temperature or general condition. The opsonic index for typhoid bacilli was reported high; that for streptococcus, low. Symptoms and signs of hypostatic pneumonia developed a few days after the blood culture was taken, and these persisted until death. About four weeks after the onset a few clots of blood were passed per rectum, and the bowels, which previously had been constipated,



showed a tendency to diarrhœa. The urine contained albumin throughout the last three weeks of the disease.

At the autopsy, the lungs showed intense congestion of both lower lobes; heart and liver were negative. The spleen was surprisingly small and hard; the mesenteric lymph nodes were not enlarged. The kidneys showed parenchymatous degeneration. The intestine showed ulcers, but not the kind seen in the fifth week of typhoid fever. These ulcers were sharply defined, having a "punched out" appearance. The edges were not raised. The bases of the ulcers were smooth and clean, and appeared to lie directly against the muscular coat. The ulcers ran in a transverse direction across the long axis of the gut. Over a few of the ulcers the peritoneum was slightly injected. Microscopical examination of the ulcers revealed nothing but what one might expect from the macroscopic appearance. No lymphoid tissue could be noted anywhere.

Dr. Moschcowitz felt that he could not account for the pathological findings; he thought that these findings could only be explained on the basis of one or two possibilities; either there was some maldevelopment of the lymphatic apparatus of the subject; or the association of the streptococcus had some effect in modifying the typhoidal lesions.

---

## LESIONS IN A CASE OF MYASTHENIA GRAVIS.<sup>1</sup>

F. S. MANDLEBAUM, M. D. AND H. L. CELLER, M. D.

The specimens to be demonstrated were obtained from a case admitted in January 1907, to the Neurological Service of Dr. B. Sachs in Mt. Sinai Hospital. The history obtained from the patient, a Russian tailor, age 52 years, contained no facts of

(1) Abstract of article published in *The Journal of Experimental Medicine*, Vol. X, 1908.

etiological significance. The course of the disease, extending over a period of seven months, was marked by the characteristic symptoms of myasthenia gravis—progressive muscular weakness with short intervals of remission, the myasthenic reaction of Jolly, and sudden death with symptoms pointing to bulbar involvement. The autopsy, performed twenty-four hours after death by Dr. Libman, revealed no gross lesions of importance in any organ but the thymus. Occupying the site of this gland and generally conforming to its outline there was a tumor 5 cm. by 3 cm. by 2.5 cm., weighing 20 grams. On section the tumor appeared lobulated, firm, and pinkish-white in color, and cells could be scraped easily from the surface.

Sections were cut from various parts of the tumor in order to determine its origin and relationship to the thymus gland proper. In only a few places could any normal thymus tissue be found. This, in some instances, was separated from the tumor by layers of connective-tissue, but in other places it was seen to be in direct relationship with the tumor. The thymus tissue has a normal appearance and contains a small number of Hassal's corpuscles, some of which show calcareous changes while others contain keratohyalin cells and polynuclear leucocytes. The tumor itself is separated from the surrounding structures by a well marked connective-tissue capsule and with the low power this is seen to extend into the tumor mass which is thus divided into numerous lobes.

Upon examination of the sections with the low power the tumor appears to be dotted with numerous slits, fissures and oval shaped openings. With a higher power it is seen that these openings are widely dilated lymph channels or lymph spaces lined with endothelium. The tumor proper is of a very dense cellular structure. The cells are quite large, of an oval, polygonal or irregular shape, and contain large vesicular nuclei with numerous chromatin granules. The cytoplasm is granular and stains lightly with eosin or picric acid. Throughout the sections the cells

have a tendency to form concentric bodies of fairly large size, somewhat resembling those found in psammoma and certain types of endothelioma, but having no direct connection with any blood vessels. As many as twelve, fifteen, or more, of these bodies may be counted in a single field. The cells in these concentric bodies are of spindle shape and their nuclei are long, narrow and curved as the result of compression. Some of the larger tumor cells contain two or more nuclei. A few cells show vacuolization of the cytoplasm, the nuclei remaining intact. A considerable number of nuclei throughout the sections show distinct nucleoli. None of the cells show any mitotic changes. A delicate stroma may be seen between the cells in those situations where the cells are less densely packed together. In some of the sections small islands of lymphoid cells are seen scattered between the tumor cells. No Hassall's corpuscles are found here, but these areas give the impression of being remnants of thymus tissue. Small masses of hyaline matter are seen here and there in the tumor, some of which are in close proximity to the blood vessels.

The lymph spaces are well filled with large spherical cells which show faint outlines and a coarsely granular cytoplasm. Most of the cells contain a small nucleus of irregular shape which is usually situated at the periphery. Besides these, smaller lymphocytic cells and granular matter are seen filling the spaces. Some of the larger cells show nuclear fragmentation. A few degenerated areas containing cholesterolin crystals are seen.

The most interesting feature is the relationship of the tumor cells to the lymph spaces and blood vessels. All of the lymph spaces are lined by endothelial cells, as has been mentioned above. In some fields it appears as though several parallel layers of proliferated endothelium surrounded a considerable portion of the lymph space. These cells always stain more deeply than the tumor cells proper and in some situations form distinct bundles of spindle shaped cells merging gradually into the tumor cells. In other places the tumor cells appear to be

springing directly from the endothelium of the lymph spaces. This is most distinctly seen where the lymph spaces have been cut more or less transversely, and in such instances the cells have a slight tendency to grow radially from their walls.

Blood vessels are very numerous throughout the tumor. These consist principally of newly-formed capillaries, though small arteries with thin walls are also present. Some of the latter show well marked hyaline degeneration. A zone of lymphocytes surrounds each capillary. This may be seen in transverse as well as in longitudinal sections. In transverse sections these cells appear as a mantle in close relationship to the capillary wall. The anatomical position of these cells can be seen very clearly in longitudinal sections. Here we have a narrow band of cells on either side of the capillary and parallel to it. The cells are seen to be bounded on one side by the endothelium of the capillary and on the other side by a second row of endothelium which must be looked upon as the outer wall of the perivascular lymph space. In other words, these cells are confined to the perivascular lymph spaces. Just beyond these cells are clear spaces due to retraction or shrinkage and bounded by the tumor cells proper. The first layer of cells grows at right angles to the vessel walls and this radial arrangement may readily be seen with the low power. They also stain more intensely than those situated at a greater distance from the vessels. There seems to be no doubt that the tumor cells originally sprung from the endothelium of the perivascular lymph spaces, from which they have become detached. The endothelium of the capillaries is normal throughout and has no bearing on the formation of the tumor.

In this connection it might not be out of place to say a few words regarding the discussion which has arisen concerning the perithelium of blood vessels and its relationship to perivascular tumors. The perithelium of the blood vessels is supposed to represent the endothelium of the perivascular lymph spaces, but in most cases it is difficult or impossible to discover the presence of



a second layer of endothelium to form an outer wall of these lymph spaces. In the usual type of perithelial growth with a radial arrangement of the tumor cells these are always closely united to the vessel wall. This is not the case in our tumor, in which a well defined zone containing lymphocytic cells separates tumor cells from vessel wall. As far as the presence of any outer endothelial boundary is concerned, a study of our case demonstrates such a layer in those sections where the capillaries are cut longitudinally. The fact that a dilatation of all the lymph vessels with marked lymph stasis is present in our case may account for the comparatively easy recognition of the perivascular lymph spaces. It is possible that many of the recorded cases of perithelioma in which the cells appear to arise directly from the adventitia of the blood vessels and where the perivascular lymph spaces are not dilated, belong in this group. Our case demonstrates the fact that tumor cells may encircle and grow radially from a blood vessel and still have no direct attachment to the vessel wall proper, but arise from an outer layer of endothelium bounding the perivascular lymph spaces.

The proper classification of this tumor is somewhat difficult. Inasmuch as the growth is perilymphatic in character, it bears the same relationship to lymphangio-endothelioma as a perithelioma does to hemangio-endothelioma. It is therefore a perilymphatic lymphangio-endothelioma.

The lesion that may be considered characteristic of myasthenia was first recorded by Weigert in 1901. This consisted of cellular foci present in a number of the skeletal muscles as well as in the heart. Confirmatory observations have been recorded by a number of subsequent investigators although agreement is lacking as to the nature of the cells of which the foci are composed. In our case the infiltrations were found widely distributed throughout the voluntary muscular system.

A large number of sections from the psoas, longus colli, deltoid, supinator longus, rectus abdominis and diaphragm were



studied and the results were fairly uniform in every muscle. The constant lesion is the presence of smaller or larger areas of cellular infiltration. In all of the muscles examined we were able to find this lesion. In most instances these areas are seen without difficulty; at other times a long search is required. The cells in these infiltrations are of small size and uniformly round in shape. Their nuclei are relatively large, usually round or slightly oval in form, and stain intensely with hematoxylin and the nuclear aniline dyes. Morphologically these cells resemble small lymphocytes. No polynuclear leucocytes, plasma cells or eosinophile cells are present in the infiltrated areas, nor can any mitotic cells be seen. In sections where the muscle fibres are cut longitudinally these areas of lymphocytic infiltration are found to be situated between adjacent fibres. The infiltrations have a tendency, in longitudinal sections, to form long, narrow bands which are easily seen upon examination on account of their intense staining qualities. In transverse sections the cellular infiltrations are cut in the opposite axis and appear as oval or roundish areas which vary considerably in size. Some may show but 15 or 20 cells while others may present ten or twenty times that number. Buzzard has suggested the term "lymphorrhages" for these cellular infiltrations, coining the word to designate that they are composed of lymphocytic cells infiltrating the muscle fibres as do red blood cells in interstitial hemorrhages. Most of the transverse sections show from one to three small capillaries in the central part of each lymphorrhage. These capillaries appear quite normal and are often filled with blood. In the longitudinal sections it is more difficult to find these small vessels unless serial sections are examined. In the study of the deltoid several longitudinally cut capillaries are seen. It is possible, in some of these vessels, to see the perivascular lymph spaces with ease, on account of the presence of lymphoid cells which completely fill the dilated lymph spaces. In one of the capillaries the endothelium limiting the outer wall of the perivascular lymph

space is clearly seen. This condition is identical with that described in the thymic tumor. The muscle fibres in the immediate vicinity of the lymphorrhages show no degenerative or atrophic changes.

Some of the muscle bundles have a tendency to stain more intensely than others, but this is frequently seen in normal muscles and can not be considered as a pathological process. The striations are distinctly seen in all sections. In some of the muscles rather prominent bands of connective tissue may be seen. Some of these bands merge directly into the muscle fibres. At these situations the sarcolemma cells are increased in number and the transverse striations are somewhat indistinct. Some of these connective tissue bands have a more or less wavy outline and show a few indistinct oval nuclei. They bear a striking resemblance to muscle fibres in shape and size and must be looked upon as a replacement fibrosis, secondary to degenerative muscle changes. This lesion is most marked in the deltoid muscle. Otherwise only a normal amount of connective tissue is present. No evidence of fatty degeneration is seen in osmic acid preparations and no pigmentation can be found in any of the muscles. A few fibres are the seat of marked degenerative changes. This is particularly noted in transverse sections of the longus colli muscle. Here the fibres stain distinctly pinkish with Van Gieson's stain, and the muscle nuclei are increased in numbers. The protoplasm is somewhat granular, quite different from the homogeneous appearance noted in ordinary hyaline degeneration. This lesion as well as that described above as occurring in the deltoid may be considered as an early degenerative atrophic change.

In the study of the psoas muscle a few small areas are seen which show a different picture. Here the sarcolemma cells are very numerous but the muscle fibres apparently are unchanged. A few cells are also present showing pycnotic nuclear changes. It is difficult properly to classify these cells, but we look upon them as polynuclear leucocytes with degenerating nuclei.

Throughout the sections the walls of the blood vessels do not show any changes whatever. The medullated nerve fibres are likewise normal, and the sensory nerve-endings ("muscle-spin-dles") which are present in some of the muscles in large numbers are apparently free from any pathological changes.

After a long search through many sections it was possible to find a few small areas of infiltration in the tongue. Apart from their small size these areas do not differ from those found in the skeletal muscles. Otherwise no changes are present, either in the muscular portion, vessels or nerves.

The occurrence of lymphorrhages in the internal organs was first reported by Buzzard, who found them most constantly in the adrenals. In our case there was a large cellular infiltration in one adrenal, and numerous smaller ones scattered throughout the liver. In the foci in the latter organ the cells seem to be grouped in or about the capillaries lying between the liver cells. It is to be noted that no degeneration of the parenchyma cells is present in the neighborhood of the lymphorrhages.

The published autopsies contain a description of many gross and microscopic lesions in the central nervous system, but the great diversity and inconstancy of these changes warrants the assumption that no pathological significance can be attached to them. Buzzard alone describes a cellular collection in a posterior root ganglion in one case of his series, that he regards as identical with those described in other tissues. In our case we have been able for the first time to demonstrate these foci in the central nervous system. A perivascular collection of lymphoid cells was present in the grey matter of the medulla near the tenth nucleus, and a number of smaller foci were found in the pyramidal tract central to the olivary body. The situation and scarcity of these lesions, however, leads us to believe that they bear no relation to the bulbar symptoms manifested clinically.

The origin of these cellular foci is still a moot question. By Weigert and by Blumer, in whose cases there was a lympho-

sarcoma of the thymus, they have been regarded as metastatic deposits. Their occurrence in cases in which no pathological condition of the thymus was present, as well as in our case, in which the thymic tumor was of endothelial nature incapable of producing lymphoid metastases, renders this theory untenable. More recently Marburg has advanced the hypothesis that myasthenia is a primary degenerative myositis, and holds the lymphoid infiltrations to be an inflammatory reaction. It has already been mentioned, however, that in our specimens the cellular foci bear no relations to the areas of muscle degeneration.

We have been able to collect from the literature forty-five cases of myasthenia gravis with more or less complete autopsy reports. It is noteworthy that in about one-fifth of this number some abnormality of the thymus, varying from simple persistence or hyperplasia to actual neoplasm, has been found. While it is manifestly impossible from these statistics to formulate a theory of the thymic origin of the disease, the relative frequency of changes in the thymus lends support to Weigert's suggestion that in a certain group of cases presenting the symptom-complex known as myasthenia gravis, the abnormally functioning thymus may play a causative role.

We are inclined to regard myasthenia gravis as a toxemia affecting not alone the muscles but all the other organs of the body as well. The influence of the thymus in producing this toxemia in a certain proportion of cases must be left an open question. A study of our specimens seems to warrant the conclusion that the lymphoid cells in the infiltrations present in the muscles and other organs are derived wholly from the dilated perivascular lymph-spaces and are an expression of the universal toxemia.

#### *Discussion.*

DR. F. C. WOOD spoke of a case of myasthenia gravis which he had recently seen at St. Luke's. Except that the thymus



was enlarged no lesions were found. There was not the slightest trace of any infiltration in the muscles or in any of the organs, so far as they had been able to determine. The thymus was approximately normal, though the germ centers were rather more developed than in an ordinary thymus. Hassall's bodies were abundant. The muscle showed no gross changes except atrophy, and it was still being sectioned in the hope that some infiltration might be found. The attempt was being made to get a satisfactory staining of the nerve endings in the muscle. Dr. Wood thought that the slight infiltration of the muscles in these cases did not account for the extreme weakness which the patients show.

DR. JAMES EWING asked whether Dr. Celler regarded the origin of the tumor from the thymus as entirely proved. Such a tumor was not at all uncommon in lymph nodes, but he had never seen it in the thymus. Of course, the thymus being a lymphoid structure might give rise to such a tumor; but as the thymus was surrounded by lymph nodes it seemed to him that one must have very conclusive evidence indeed of the thymus origin before this could be claimed.

DR. HORST OERTEL asked whether the suprarenals showed any lesions in this case, and whether the chromaffinic system had been studied.

DR. CELLER, in answer to Dr. Wood, said that he had not meant to convey the impression that the lymphocytic infiltration was the cause of the muscular weakness. He had concluded that the disease was probably a toxemia of unknown origin which might, in some cases at least, arise from an abnormally functioning thymus gland. As regarded the origin of the tumor, while in some specimens uninvaded thymus tissue was preserved, in others a direct connection between the remains of thymus tissue and the tumor could be demonstrated. It seemed to him that if this were a tumor arising in the lymph nodes it would not have infiltrated the thymus alone, but would have invaded



other structures as well. In this case the thymus alone was involved. Furthermore, the tumor apparently occupied the central portion of the organ, whereas the areas of normal thymus tissue were found only at the periphery. The chromophilic system, as far as the adrenals only were concerned, was studied, but no changes were found.

---

## TWO ATYPICAL KIDNEY TUMORS.

I. STRAUSS, M.D.

Dr. I. Strauss presented specimens of two atypical kidney tumors. The first was a kidney removed at operation by Dr. Ladinsky, which on examination proved to be a form of hypernephroma, showing marked cystic degeneration, and on section was of a glandular type. The tumor was sharply encapsulated. The condition of the adrenal was not ascertained. In many places it was difficult to determine the nature of the growth, but in certain parts it showed a typical perithelioma structure.

In a recent paper Stoerck pointed out that he was not able to find any evidence of a lumen in the adrenal in the human subject, and stated that he thought that the lumen reported in the adrenals of dogs and horses was due to a hemorrhage. In adrenals fixed in Orth's fluid the contents of the lumina were wanting, but when the organs were fixed in Zenker's solution there were present either evidences of blood or serum. He intimated that in the future he will side with those pathologists who consider this form of hypernephroma due, not to adrenal rests, but to some other form of growth.

The second case was a kidney also removed at operation. The patient had suffered from pyuria. In the pelvis of the kidney there was a calculus about 1 cm. in diameter. All these cavities

led down into the pelvis and their walls were necrotic. Streaks of firm yellow tissue were seen radiating out from these cavities and making a slight prominence under the capsules. When a section was taken of this part of the tumor it showed a structure very similar to a hypernephroma. The cells were vacuolated and their nuclei were in the center. They were arranged in rows and sometimes along the walls of a capillary. The cells did not react to osmic acid, but did to Sudan III.

Two pathologists had made a positive diagnosis of hypernephroma. Dr. Elser had called attention to the fact that at the New York Hospital he had had a case in which there was a tumor of the axilla. The surgeon had cut down on the supposed tumor and had sent specimens to the laboratory. On examination these same fat cells were found. Further examination proved the tumor to be due to gauze left in the axilla. These fatty cells might be a peculiar reaction of the fat to the stimulus of the foreign matter. It was possible that this tumor might be some of the pelvic fat which had undergone this peculiar degeneration, and grown out into the cortex, and that we had to deal with a simple pyonephroma. The tumor was full of lymph follicles showing typical structure of lymph gland. The specimen was stained for tubercle bacilli, but none was found.

### *Discussion.*

DR. C. W. FIELD asked Dr. Strauss whether any chemical analyses had been made to determine the relation between the cholesterin and the lecithin content of the cells. In these inflammatory conditions one should be able to detect the normal relationship between the various fats and determine their origin in this way.

DR. STRAUSS said that such analyses had not been made.

DR. F. C. WOOD said in regard to the inflammatory case and also in regard to the tumor of the axilla which had been spoken

of, that one must always consider the possibility of such appearances being due to growing fat cells. In examining specimens of chronic inflammation from the broad ligament and pelvic tissues, he had noticed a large number of cells which looked like hypernephroma cells, but which on study proved to be regenerating fat cells. He had seen the same phenomena in other cases where hypernephroma could be excluded, for instance, in a case of adenoma of the breast. The bodies of the cells were granular or reticulated, and there were usually no discrete fat globules of any size in these cells. A chronically inflamed breast showed quite large multinuclear cells which had led to an erroneous diagnosis of giant cells and hence tuberculosis. The same was true of peritoneal inflammatory tissue. He had seen areas which looked so much like hypernephroma that one would consider them hypernephroma of the broad ligament. He thought it was not the custom to think of fat cells as anything but cells containing large quantities of fat, whereas these growing fat cells, for instance in the omentum, were very peculiar and looked very much like hypernephroma until they had collected their normal amount of fat. The same thing was found in the bone marrow in cases of osteomyelitis.

---

#### AGGLUTINATING ACTION OF RICIN ON ERYTHROCYTES IN ISOTONIC SUGAR SOLUTION.

C. W. FIELD, M.D.

Dr. Cyrus W. Field reported an interesting phenomenon which he had recently observed. Last year he had spoken to the Society of some work done in the past four or five years on the agglutinating reaction in bacteria, showing that the agglutinin reaction does not take place between dialyzed bacteria and dialyzed serum, but that electrolytes must be present.

In working with the red blood cells suspended in isotonic salt solution, there is naturally a large quantity of electrolyte present, and on the addition of ricin the cells are agglutinated. An interesting fact was that if the cells were washed in isotonic sugar solution three times and suspended in this mixture, and the ricin added, no agglutination took place, that is, if the agglutination tests were made immediately after the last washing. If the blood cells were allowed to stand for twenty-four hours or longer in the isotonic sugar solution, and the ricin then added, they agglutinated readily.

If to the isotonic sugar solution was added 1-10,000 normal sodium chloride solution, the agglutination took place immediately.

Without going into a discussion of the factors which brought about agglutination, Dr. Field said that he believed there was a passage of electrolyte through the envelope of the red cell into the surrounding fluid. This conclusion was practically opposed to all the work of Stewart, of Chicago, who as the result of his experiments has claimed that the envelope of the red cell is impermeable to the electrolytes. Nevertheless, Dr. Field believed that the phenomenon spoken of pointed very strongly to the fact that there was a passage of the electrolytes from the cells to the surrounding medium.

## A REPORT ON MOUSE TUMORS.

J. W. JOBLING, M.D.

I wish to speak of certain results obtained during the last two years from the transplantation of mouse tumors. The results to be referred to were obtained with twenty-two tumors which had developed spontaneously in mice. The mice were pur-

chased chiefly from breeders. With the exception of three, all the tumors could be classified as adenocarcinomata, though one showed an almost solid growth of epithelial cells throughout the tumor.

Of the twenty-two tumors, three were obtained so recently that they are not included in the number developing when transplanted into other mice. Of the nineteen remaining, sixteen, or 84.2 per cent., developed tumors upon transplantation into other mice.

Seventeen of the tumors were composed of epithelial cells. They can be divided into two classes, namely, hemorrhagic and non-hemorrhagic. This division is made because some investigators claim that the hemorrhagic type of tumor is more difficult of successful transplantation. The incubation period—the time intervening between inoculation and appearance of tumor—was longer and the percentage of retrogressions greater, in our experience, than in those tumors which developed from the non-hemorrhagic precursors. In one series of ten hemorrhagic tumors, seven, or 70 per cent., were successfully transplanted, but of these, all the tumors in three strains underwent retrogression before they had become large enough to enable us to make further transplantations.

There were seven non-hemorrhagic tumors which were successfully transplanted into other mice, but all the tumors in two strains underwent retrogression in the first generation before they could be transplanted.

The average incubation period in the case of the hemorrhagic tumors was seventy-two days; of the non-hemorrhagic tumors seventy days. The longest incubation period noted was 150 days which occurred with two tumors, one being hemorrhagic and the other non-hemorrhagic. The average number of tumors developing in the first generation with the hemorrhagic tumors was 7 per cent., and with the non-hemorrhagic 9.5 per cent.



It has also been stated that but few of the mice with spontaneous tumors show lung metastases. Apolant reported that he found six examples of lung metastases in 221 mice.

Of our series, eight, or 42 per cent., of the nineteen cancer mice showed macroscopical lung metastases. Dividing these into two series as before, we have four, or 40 per cent., showing lung metastases in the hemorrhagic and four, or 44 per cent., in the non-hemorrhagic type. The tendency is about equal in both.

I wish now to speak of three mice, each of which had more than one tumor. The difficulty encountered in these cases in determining what should be called a metastasis, and what an original growth, is considerable. The first mouse exhibited a large tumor in the left inguinal region which was an adenocarcinoma, and a small flat nodule a little anterior to the right axillary space, which was adenomatous in structure. The second mouse presented a large solid alveolar carcinoma in the right inguinal region and a second tumor in the lower lobe of the right lung—apparently identical with a tumor which Tyzzer has described as a papillary cystadenoma which he found in the lungs of two mice. The third mouse showed three tumors. The largest of the three was attached to the side of the neck and was hemorrhagic; the second was in the right inguinal region; the third, the smallest, was in the left inguinal region. Neither of the latter was hemorrhagic. Mice inoculated with material from the hemorrhagic tumor developed hemorrhagic tumors, while mice inoculated with material from the non-hemorrhagic tumor in the right inguinal region developed non-hemorrhagic tumors.

Finally, I wish to refer to three mice, two of which presented tumors composed of lymphoid tissue and one a tumor of a spindle cell sarcomatous nature. The first of these was a mouse showing general hyperplasia of the lymphoid tissue. In the neck there were two large masses each measuring about 1.5 cm. in diameter; in both axillary regions, masses measuring 7

mm. and in addition masses in the left inguinal region, mesentery and retroperitoneal tissues. The condition resembled the so-called malignant lymphoma of Haaland. Haaland reported six instances, but in no case did he obtain any growth in other mice inoculated with the tumor material. But he states that, after placing normal mice in the cage with a mouse having lymphoma, five similar tumors appeared within two years. With the material from the mouse mentioned, I inoculated 100 mice and, up to the present time, one of these has developed a tumor which, histologically, is identical with that used for inoculation.

The second mouse also had a tumor of lymphoid structure. In this mouse there was no general hyperplasia of lymphoid tissues. It is too soon to say if tumors will develop in mice inoculated from this tumor.

The last mouse, presenting a spindle cell sarcoma on the left side of the chest, has come into my hands so recently that no report can yet be made upon the results of its transplantation.

### *Discussion.*

DR. CHARLES NORRIS said that from an examination of the mouse with the axillary tumor and the lung tumor, it certainly seemed as though there were two different tumors. He had been much interested in the general lymphosarcoma of the mouse, and thought that that line of tumors would be the most fruitful as far as etiology was concerned.

## A CASE OF TUBERCULOSIS IN A CAT.

A. F. HESS, M.D.

Dr. A. F. Hess showed a case of tuberculosis in a cat which had been sent to the Department of Health laboratory to be examined for rabies. No Negri bodies could be found, but the

autopsy disclosed marked tuberculosis of both lungs with enlargement of the mesenteric glands. There were no lesions in the intestine and stomach, and the only other lesions were marked petechial hemorrhages throughout, in the kidney, mesentery, pleura, and meninges.

The history showed that the cat had been in the family for three months; it had not been well and was considered lazy. It had been fed on raw milk as well as other things. There were no tuberculous individuals living in the house. The only symptom pointing to the involvement of the lungs was a cough which the cat had had for some time.

On looking up the literature, Dr. Hess had found that Abel of Leipzig had made autopsies on cats sent to him with symptoms suggesting tuberculosis, and that among four hundred cats he found nine cases of tuberculosis. The only case Dr. Hess had found in which the bacillus was isolated, differentiated, and cultivated, was one where the human type of bacillus was found.

---

## NOTES ON BLOOD CULTURES IN HUMAN GLANDERS.

BURRILL B. CROHN, M.D.

The following notes on blood cultures in human glanders have been collected after a fairly complete search through the literature on that subject, and include the data obtained from a case which was admitted to Mt. Sinai Hospital in August, 1907.

In regard to blood cultures in glanders the literature is rather meagre in cases in which this diagnostic aid has been utilized. Most of the cases have been studied very completely from the clinical and also the pathological standpoint, but in only a few cases has an attempt been made to cultivate the *Bacillus mallei*

from the blood. I have collected fourteen reported cases of glanders or farcy; our own case not yet in the literature, makes the fifteenth. These cases are divided clinically, on the basis of duration of the illness, into acute and chronic glanders or farcy. (It should be noted that the clinical subdivision of this disease into two classes, namely glanders and farcy may be disregarded in this paper as all the cases under discussion have shown practically only one picture, namely a combination of the type called farcy with that of glanders, the former predominating throughout the course.) The clinical histories in these cases correspond very closely. There is almost invariably a history of exposure to glandered horses. In four of the cases there was an actual point of inoculation on the hand; the onset was acute with sharp pain in the lower thorax, fever, chills, malaise, general prostration. Initial symptoms referable to the lungs is the rule in over 80 per cent. of the cases. The picture of a general pyemia supervenes rapidly, or is present from the beginning; numerous subcutaneous and intramuscular abscesses form, followed later by a pustular rash; there is increased prostration, rapidly developing delirium or coma, and death in from ten to thirty-six days. The picture is invariably one of a profound pyemia and toxemia with early or late lung involvement. The localization of the infection in the upper respiratory passages, so characteristic of glanders in the horse is rarely seen in man, in whom the picture of a farcy, that is accentuation of the localized point of inoculation with rapidly developing blood invasion and the establishment of metastatic foci in the muscles and joints predominates.

Of the fifteen cases under discussion to-night there are thirteen acute and two chronic cases. Of the thirteen acute cases ten gave positive blood cultures. Of the three cases of acute glanders in which the organism was not recovered from the blood, one case reported by Woodcock should be disregarded as the subsequent bacteriology of the whole case was not satisfac-

torily nor conclusively worked out; nor was the organism from the lesions proved beyond a doubt. Of the ten positive cases, the blood culture was obtained when the disease was well advanced in its course. The earliest culture taken in our own case was on the seventh day of the disease, the total course being only eleven days; the remainder of the cultures in the series were taken from one to four days before death. In all but one of the cases there were already established numerous metastatic abscesses and active lung signs; in six out of the ten the pustular rash had already made its appearance. In all the cases at the time of culture, there was marked prostration, high continuous fever, rapid pulse, and other signs of an intense infection.

Looking over the two cases of acute glanders with negative results as to blood cultures (omitting from the discussion Woodcock's case), it is noted that these cases correspond in their clinical picture fairly accurately with those in the previous series of positive results, the only difference being in a somewhat longer duration of the disease, and a less rapid appearance of the local pyemic foci. In these two cases the attempt to isolate the organism from the blood was made earlier in the course of the disease than in the previous series; in the first case, Gutowski's, on the 13th day (total duration 27 days); in the second, Potter's case, on the 21st day (total course 35 days); in neither case was the generalized pustular rash evident at the time of the blood culture. The case reported by Van Ingen is of special interest for the reason that two blood cultures taken respectively on the 23rd and 25th day of the disease were negative, though lung involvement and numerous metastatic abscesses were present. A blood culture taken on the 30th day, two days before death, and the day just preceding the appearance of the pustular rash, was positive.

Of the two chronic cases, both with negative blood cultures, that of Post had run a course of nine months with lung and



metastatic foci but no pustular rash. (The patient was still living at time of publication of his paper.) That of Sieur ran a course of two and a half years following a local infection of the finger and presented the symptoms of a chronic pyemia without lung or cutaneous signs except toward the very end.

### *Conclusions.*

The deductions to be drawn from a study of those cases of human glanders with blood cultures is as follows: In acute cases, cultivations from the blood early in the course of the disease are likely to be negative. Those taken later in the course, particularly at the time of and after the appearance of the pustular rash, are invariably positive; chronic cases give negative results. These conclusions are singularly in contrast with the results obtained by workers in the field of equine glanders. MacFadyean, an eminent authority on this subject, writing in the *Glasgow Journal of Comparative Pathology and Therapeutics*, says: "The glanders bacillus is a tissue parasite and in all cases of glanders in the horse it is almost entirely confined to the lesions and the discharges from them. It is no doubt transported by the blood as well as lymph channels, but the disease in the horse is never septicemic. Even in the acute case the bacilli are so sparingly present in the blood that their discovery by microscopic and cultural methods is nearly always impossible, and even considerable quantities of blood fail to transmit the disease by inoculation."

The explanation of this apparent inconsistency is, that the disease in the horse rarely, if ever, runs so acute a course as it does in man, manifesting itself mainly as a subacute or chronic affection of the respiratory apparatus or as a localized farcy of the skin and related lymph organs. The corresponding type in man that of the so-called chronic glanders, gives, as we have seen, similarly negative blood cultures. The usual picture in

man, however, is that of a rapidly developing and grave pyemia with a less considerable and slower involvement of the related lymphoid apparatus, but with the rapid development of metastatic muscle, bone and joint foci which can only have been transmitted by the blood current. It is quite probable that the bacteria are present in the blood in human cases early in the disease, in fact, as early as the first metastatic deposit makes its appearance, but probably they are in such few numbers that our present methods are incapable of demonstrating them. It is in the later stages of the disease when the bacteria become much more numerous in the blood (as evidenced by the outbreak of a general pustular rash, the pustules containing the bacilli), that we are successful in cultivating them from the blood. In the chronic cases, those which present the picture of localized glanders of the respiratory tract, the blood is probably sterile; in those cases with the establishment of farcy buds and metastatic foci, it would perhaps be possible to cultivate the organisms from the blood if the attempt were made just at the time of the new outbreak; between the recurrences of localized depositions peripherally, attempts at isolating the specific organism from the blood would probably be unsuccessful.

As to the nature of the bacillemia the same question arises here as arises in the discussion of the mode of infection of the blood current in typhoid fever. Is it a true bacteremia or is it an overflow? In speaking of typhoid, Coleman and Buxton think that the bacillemia is secondary to the infection of the lymphoid apparatus of the gastro-intestinal tract and is an overflow from the lympho-poetic system. Whether the infection of the blood stream in glanders is analogously the result of an overflow from the lymphatic involvement which invariably accompanies the local lesion is one view; if we accept the hypothesis of the possibility of a primary infection of the lungs and respiratory tract by inhalation, we must suppose the bronchial glands to be the source of overflow in most of our cases.

On the other hand, the recent work of Duval on "Vascular Lesions in Experimental Glanders" shows that there is a marked reaction of the vessel wall to the specific toxin, and that thrombosis of the vessels in the neighborhood of the point of inoculation occurs. In the light of these facts it may be supposed that the metastatic foci and free bacteria have a common origin in these thrombi, and that the metastatic deposits result from minute thrombotic emboli, although it must be stated that true infarcts or secondary foci in those organs in which they usually are found have not been demonstrated in glanders. A third view, that it is a true bacteremia, may be considered, since in our case the second blood culture taken two days after the first showed an increase in the number of bacilli present. We must suppose on this hypothesis that human glanders is a bacteremia the source of which is usually the lungs or respiratory tract, and in which the circulating bacilli establish by preference pyemic foci in the muscles and joints.

*Prognosis.*—Unfortunately the prognosis as judged by positive blood culture, is about the same as that held for the appearance of a pustular rash; that is, fatal.

---

# Proceedings of the New York Pathological Society.

---

New Series, Vol. VIII.      OCTOBER and NOVEMBER, 1908      Nos. 5 and 6

---

## TABLE OF CONTENTS

BUERGER, Two Interesting Types of Bone Sarcoma.—PEARCE, Bone Formation in the Kidney after Partial Extirpation.—EPSTEIN AND OTTENBERG, A Simple Method of Performing Serum Reactions.—WOLFF-EISNER, Theoretical and Practical Considerations Concerning the Significance of the Conjunctival Reaction (Ophthalmic Tuberculin Test).—CARLISLE AND MARTIN, A Case of Typhoid Fever Associated with Cholelithiasis, Chronic Suppurative Cholecystitis, and Hepatic Abscesses.—WOOD, Adenomyoma of the Round Ligament.—CELLER, Specimens from a Case of Gastro-Intestinal Pseudoleukemia,—LONGCOPE, A Study of Cases of Hodgkin's Disease and Lymphosarcoma.

---

DR. E. LIBMAN, *President.*

---

## TWO INTERESTING TYPES OF BONE SARCOMA.

LEO BUERGER, M. D.

The two specimens which I am about to present to you are of interest both to the pathologist and to the clinician. They show rather unusual types of myelogenous sarcoma, one developing in the upper end of the tibia, the other in the lower part of the femur. Most of the myelogenous sarcomas of the long bones are of the soft variety, and are often vascular and hemorrhagic, sometimes the seat of cystic or hemorrhagic softening, and usually attended by expansion of the bony cortex.

The two tumors to which I wish to call attention, belong to the *osteoid sarcomas*, one being almost of the pure osteoid variety, the other combining a fibro-sarcoma with the osteoid type of growth. Both of these present certain features in common: they have grown diffusely in the spongy bone without showing any tendency to disintegration; they are the site of marked calcification and ossification; expansion of the bony cortex is absent; and, in both cases, after producing extensive change in the interior of the bone itself without causing visible external manifestations, the tumors have perforated the cortex of the bone and produced fairly large rapidly growing extra-osseous tumors.

The first specimen, an osteoid sarcoma of the tibia, was taken from a boy of seventeen, operated on by Dr. Gerster of Mt. Sinai Hospital. There was a history of a slight sprain three months previous to amputation, but the tumefaction in the neighborhood of the knee was observed for only about a week.

*Description of the tumor:*—The upper and outer aspect of the leg in its upper fourth is occupied by an ovoid swelling. In this region there is an exploratory incision, the fascia muscles have been cut and in the depth of the wound soft, bloody tumor tissue is found. The muscles of the leg over the tumor are slightly thin and stretched, and somewhat edematous; and the deeper layers show beginning infiltration by soft grayish (probably tumor) tissue. Occupying the external surface of the tibia and traversing the shaft at one place so as to cause slight tumefaction posteriorly, there is an ovoid sessile tumor extending from the epiphyseal line downward for about four inches. At the middle of this mass the growth is thickest, about one and one-half inches. Upon section of the tibia we see that the tumor may be divided into a periosteal and a medullary portion. The periosteal consists in the main of a calcific or bony mass which forms a large part of the extra-osseous tumor and which can be traced through the thinned out remnants of the cortex into a similar sclerotic or calcific tumor in the head of the tibia.



Capping this hard periosteal tumor, is the soft infiltrating and partly disintegrated ovoid mass previously described. The medullary part of the tumor is also for the most part stony hard in consistency, infiltrates the whole of the upper end of the diaphysis, and shows no evidences of soft tumor tissue until a point in the shaft about five inches below the epiphyseal line. Here, although still retaining a slightly osseous nature, the sclerotic tissue seems to be mixed with softer elements which give it the appearance of true tumor. The tumor ends abruptly at a point just below the middle of the shaft. We have here then a new growth which has probably originated somewhere in the upper end of the diaphysis, and which has diffusely infiltrated the cancellous bone and has been almost completely converted into a hard stony mass. Although its relation to the extra-osseous growth is not perfectly clear at all points, it is fair to assume that perforation of the cortex had occurred in a number of places and that a growth was produced which possessed the tendency to sclerosis which was characteristic of the primary growth. Having attained certain dimensions, the character of the tumor tissue suddenly became altered and rapid proliferation around the tibia took place causing a large soft typical sarcoma mass.

Microscopically we may divide the tumor into two parts, the hard and the soft portions. The soft portions show rather typical osteoid sarcoma with a predominance of the cellular elements and in places large collections of giant cells. Here and there islands of atypical cartilage formation can be observed. The sclerotic parts show a diffuse calcification either of well defined masses of osteoid ground substance or diffuse deposits of calcium salts poorly differentiated in the cellular substance.

From the standpoint of the pathologist, the specimen, therefore, is of interest because it shows the sudden change of a calcifying, osteoid growth poor in cells, a tumor of slight malignancy, into a rapidly growing soft cellular variety, in which the histological picture is quite different from that found in the main tumor mass. When reporting to the surgeon, therefore,

on excised portions of soft extra-osseous sarcomas, we must bear in mind that whenever osteoid or cartilaginous tissue is present, there may be a calcifying or ossifying diffuse tumor growth in the bone itself.

Clinically, sclerosing tumors of this type are of interest because they might be diagnosticated by the X-ray picture long before the alteration into soft variety occurs, and before marked external deformity is present.

In the second specimen the difference between the character of the extra-osseous and the medullary growth is even more striking. Here in a large tumor of the lower end of the femur, the sections removed for diagnosis from the soft parts were of the osteoid and chondroid sarcoma variety, and we were rather surprised to find that practically the whole of the myelogenous growth belonged to the fibro-sarcoma type.

*Description of the tumor:*—Occupying the anterior and inner aspect of the lower end of the femur there is an ovoid tumor about the size of a large fist, its most prominent part corresponding to a point just above the internal condyle. In front, it extends completely across the femur, and upward for about two inches above the articular surface. In this situation, the tumor is one and one-half inches thick, and pearly and gritty on section, and can be traced directly into the medullary cavity through an irregular opening one cm. above the articular surface. On the internal aspect the tumor has been incised and shows evidences of disintegration and hemorrhage. Here it is made up of a number of lobulated nodules disposed around a stalk of dense osseous tissue which has its base at the adductor tubercle and which is part of the diffuse ossifying process that occupies the adjacent portions of the shaft and lower end of the bone. On section of the bone we find that the cancellous tissue is everywhere infiltrated by tumor of cartilaginous consistency. Although the cortex is somewhat thinned in places, there is no expansion. Perforation of the cortex has occurred in a number of places, the largest being anteriorly, from which point the extra-osseous tumor has probably originated. In the inter-

condylar notch the tumor has caused a prolapse of the synovial membrane, but has not as yet entered the cavity of the joint. The shaft of the femur is also infiltrated and the upper end of the tumor can be easily separated from the normal marrow by a zone of hemorrhage five inches above the intercondyloid notch.

Here too then we have a diffusely growing tumor starting in the end of one of the long bones, producing a diffuse infiltration of the cancellous tissue and shaft, becoming partly ossified and calcified, manifesting this tendency in part of the extra-osseous growth, and finally changing its character into a rapidly growing soft variety.

Microscopically the medullary portion shows fibro-sarcoma, the production of fibrous intercellular substance preponderating except in those places where the tumor has recently perforated the cortex and shows evidences of rapid growth. A part of the extra-osseous growth is calcified but in the main it presents a new picture, namely, a combination of osteoid sarcoma and chondroid sarcoma with areas in which the predominance of the cellular elements are of so striking a feature that the osteoid tissue is difficult to find.

The two tumors, then, resemble each other in the presence of osteoid portions, in the tendency to sclerosis, in the absence of expansion of the bone, and in the transformation of type occurring in the extra-osseous growth. Here, too, a diagnosis by means of the X-ray could probably have been made long before there were any external signs.

I have brought with me another specimen of osteoid sarcoma because it shows quite a different development. Here you see a small soft growth in the lower end of the femur, which soon penetrated the bone and produced a large mass in the soft parts. This was evidently a rather malignant type in which the absence of calcifying and ossifying changes may be held accountable for the rapidity of its advance.

---

BONE FORMATION IN THE KIDNEY AFTER PARTIAL  
EXTIRPATION.

RICHARD M. PEARCE. M. D.

Dr. Richard M. Pearce showed some sections illustrating heteroplastic bone formation in the kidneys of dogs. The condition was found in the course of some experiments which had for their object the reduction of the kidney of the dog to a minimum compatible with life. The injury consisted of a transverse bisection of the kidney; the new bone was found in the newly formed tissue resulting from this injury. It occurred in six kidneys in a series of fourteen dogs, after periods, respectively, of twenty-two, thirty-three, thirty-five, forty-eight (2), and 164 days. The facts to which Dr. Pearce wished to draw attention were, in the first place, that with the exception of the rabbit's kidney, heteroplastic bone formation had not been observed in the kidney of any animal. There were no records in the literature of its appearance in the kidney of man. There were four observations concerning bone formation in the rabbit's kidney after ligation of the renal vessels (Sacerdotti and Frattin, Poscharisskey, Maximow, Liek). These experiments were based on Litten's well known observation that ligation of the renal vessels is followed by necrosis and calcification of the kidney substance with the ingrowth of granulation tissue from the capsule. Calcification and granulation tissue appear to be the important factors in new bone formation, and this was obtained by the observers quoted in about 60 per cent. of their animals.

Liek had attempted to produce the same condition in cats, but without success. He commented on the fact that this bone formation in the kidney had been found in no animal except the rabbit and offered as a possible explanation the low calcium content of the blood of most animals as compared to that of the rabbit, the percentage being 1.62 for the rabbit, against 0.077 for the dog. The observation of the occurrence of bone formation in the dog's kidney, here presented, did not support Liek's explanation.

Another point was the occurrence of bone in the simple repair of the slight necrosis following partial extirpation, as contrasted with its occurrence in the repair of diffuse necrosis following ligation.

A third point was the type of ossification, that is, the formation of bone directly in connective tissue without evidence of previous deposition of lime salts.

An important point also was the occurrence, in each of the six kidneys, of the new bone immediately under the pelvic mucosa and nowhere else. For this localization no explanation could be offered.

The literature on the general subject of heteroplastic bone formation had recently been well covered by the papers of Bunting and Buerger and Oppenheimer.

## A SIMPLE METHOD OF PERFORMING SERUM REACTIONS.

ALBERT A. EPSTEIN, M. D., AND REUBEN OTTENBERG, M. D.

Dr. Reuben Ottenberg presented for Dr. Epstein and himself a simple method for performing serum reactions, and added a few remarks on some interesting results which had been obtained.

The method arose in the first place from the necessity of testing for hemolysis in cases in which transfusion of blood was proposed. Since the work of Drs. Beebe and Weil on the hemolytic effects of malignant tumors, since Crile's report of very frequent hemolysis by sera of cancer patients, and since Pepper's report of a fatal case of hemolysis following transfusion, it has been well recognized that hemolysis, though not common, does occur on mixing human bloods. Pathologists are now called upon to examine the blood of persons on whom a transfusion is to be performed. To do this test it has usually been necessary



to secure several cubic centimeters of blood. In practice, however, it has often been impossible to do this, either on account of the urgency of the case, or of the fact that the patient was an infant. For this reason, the present method, which is practically an application of Wright's opsonic technique, has been evolved. The method requires but a few drops of blood, and can be carried out very quickly.

The things required are:

1. Glass capsules made of small caliber tubing (4 to 5 mm. in diameter) drawn out at both ends into fine capillaries.
2. Pipettes made of glass tubing (6 to 8 mm. in diameter). These are fitted with nipples.
3. Pipettes like the above but made of tubing of 4 to 5 mm. in diameter.
4. Normal salt solution (0.85 per cent.) to which 1 per cent. of sodium citrate has been added.

In obtaining the blood, the lobule of the ear is pricked with a needle. To prepare the suspension of red blood cells, the blood which oozes out is drawn up to an arbitrary mark on the first stem of one of the larger pipettes. This blood is then diluted by drawing into the same pipette successive portions of the salt-citrate solution up to the mark, allowing a small bubble of air to intervene between the portions. The blood can thus be diluted to any desired extent; usually a 1-10 dilution is used. After the blood and the citrate solution have been thoroughly mixed by running the two up and down in the pipette, the tip of the pipette is sealed in the flame. If desired, this pipette can then be used as a centrifuge tube and the blood cells washed in salt solution until free of serum. In practical tests before transfusion, however, this is not necessary, as after transfusion itself both sera are present in the vessels of the recipient.

The serum for the test is obtained by immersing the tip of the glass capsule in the issuing drops of blood. The capsule fills itself by capillary action. When the capsule is about three-quarters full, its free end is sealed in the flame. The capsule is then centrifuged, and clear serum is obtained in a few minutes.

(To make the test even more practical, so that it can be carried out at the bedside, Dr. Epstein has devised a small portable hand centrifuge.)

To carry out the test, equal volumes of serum and red blood cell suspension are mixed in the smaller pipettes described above; the capillary ends of the pipettes are sealed; and the mixture is then incubated at  $37.5^{\circ}$  C. for one to two hours. Observations are then made.

Of the ninety cases tested up to the present the results so far as hemolysis is concerned will be presented in a future communication.

One thing, however, seems to deserve discussion here; namely, the possible role of agglutination in transfusion. Up to the present, this point, though mentioned by Hektoen, has not received sufficient consideration. The reaction of agglutination is so striking as to lead to the thought that agglutination might be a danger in transfusion. Though there is no conclusive evidence on the subject, this might account for some of the unfavorable results in transfusion. Dr. Pearce has shown in experiments on dogs, that the injection of agglutinative sera causes severe symptoms and frequently death, due to thrombi of agglutinated red blood cells in the liver. Whether or not this is a real danger in transfusion remains to be settled by further investigation.

Tabulation of the agglutinations was begun simply to find out whether the results of the tests were reliable and would coincide with those of other observers. The beautiful way in which the bloods of various persons arranged themselves in sharply defined groups was very striking.

It was first pointed out by Landsteiner, and later by Hektoen, Gay, and others, that according to the mutual agglutinations of their sera, bloods could be divided into three classes, defined as follows:

1. In the first group the red blood cells are not agglutinable by any other blood, although the serum is found to agglutinate the red blood cells of all persons not of this group.

2. The second group is agglutinated by the first and third groups, but it agglutinates only the third group.

3. The third group is agglutinated by the first and second; but it agglutinates only the second group; occasionally also members of the third group.

This grouping was remarkably regular. Out of all the tests there was really not one blood which did not fit into it. There was one exception in which with repeated trials the red blood cells of group 2 were not agglutinated by the serum of a blood which clearly belonged to group 1, since it was not agglutinated by any other blood.

The explanation of this grouping is very much in dispute, and several theories have been put forward. Gay has tried to prove that the grouping is due to differences in tonicity of the serum. Hektoen, on the other hand, believes that there are different specific agglutinating substances, and that a given blood may possess one or two or none of them. His view, which seems the more reasonable, is supported by his absorption experiments, in which after the agglutinating power of a serum for the red blood cells of one class had been absorbed by an excess of red blood of that class, the serum still retained its agglutinating power for red blood cells of another class.

The coincidence of a brother and sister, whose bloods were examined, belonging to the same agglutination group, led the authors to inquire whether this blood characteristic, which from the work of Hektoen and Gay seems to be a permanent characteristic of the individual, is hereditary. Hektoen tested a family, and found that the mother and three of the children belonged to group 1, and the remaining child to group 2. The authors tested two families. In the one the mother and seven children were all found to belong to group 2; the father could not be examined. In another family, mother, father, and four children all belonged to group 3. It seemed probably a coincidence that the father and mother were of the same group, but possibly a matter of heredity that the children were.

Before any definite conclusions can be reached on this point

## AGGLUTINATIONS

## RED BLOOD CELLS

	I							II			III				
	52	53	54	55	56	57	45	46	42	43	50	47	48	49	
I	—	—	—	—	—	—	—	+	+	+	+	+	+	+	Second Family
	—	—	—	—	—	—	—	+	+	+	+	+	+	+	
	—	—	—	—	—	—	—	+	+	+	+	+	+	+	
	—	—	—	—	—	—	—	+	+	+	+	+	+	+	
	—	—	—	—	—	—	—	+	+	+	+	+	+	+	
	—	—	—	—	—	—	—	+	+	+	+	+	+	+	
	—	—	—	—	—	—	—	—	—	—	—	—	—	—	
II	46	—	—	—	—	—	—	—	—	—	—	+	+	+	Brother and Sister
	42	—	—	—	—	—	—	—	—	—	—	+	+	+	
	43	—	—	—	—	—	—	—	—	—	—	+	+	+	
	50	—	—	—	—	—	—	—	—	—	—	+	+	+	
III	47	—	—	—	—	—	—	+	+	+	+	—	—	—	
	48	—	—	—	—	—	—	—	—	—	+	—	—	—	
	49	—	—	—	—	—	—	—	—	—	—	—	—	—	

S E R A

		AGGLUTINATIONS																			
		I										II									
		REID BLOOD CELLS										First Family									
		25	26	28	30	31	34	27	29	32	33	35	36	37	38	39	40	41	42	43	44
I	25	—	—	—	—	—	—	+	+	+	+	+	+	+	+	+	+	+	+	+	+
	26	—	—	—	—	—	—	+	+	+	+	+	+	+	+	+	+	+	+	+	+
	28	—	—	—	—	—	—	+	+	+	+	+	+	+	+	+	+	+	+	+	+
	30	—	—	—	—	—	—	+	+	+	+	+	+	+	+	+	+	+	+	+	+
	31	—	—	—	—	—	—	+	+	+	+	+	+	+	+	+	+	+	+	+	+
	34	—	—	—	—	—	—	+	+	+	+	+	+	+	+	+	+	+	+	+	+
	27	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	29	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	32	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	33	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
II	35	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	36	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	37	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	38	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	39	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	40	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	41	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	42	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	43	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	44	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—

— S E R A —

First  
Family



a great deal of careful work must be done, and the authors hope to present further studies later on. It seems, however, from the sharply opposed nature of these blood characteristics that if they are inherited at all they will form a very good example of the Mendelian law of heredity.

*Discussion.*

DR. S. P. BEEBE asked whether or not it had been possible by the use of this method to detect any dangerous elements in transfusion and prevent dangerous transfusions; or whether any transfusion had been made in a case where this test showed hemolysis to exist, and if so, what results had followed.

DR. OTTENBERG said that they had not yet been able to use this method in any cases which had been followed by transfusion. They had been working on it for only three weeks. Before that the tests were done in the ordinary way. In one case in which hemolysis was detected the proposed transfusion was not done. Dr. Ottenberg said that he knew of one case in which slight hemolysis was detected, and yet the transfusion was done. It was followed by some hemoglobinuria, etc., but nothing serious resulted. Evidently hemolysis was not always a contraindication. Nevertheless tests should always be made and a marked hemolysis should be regarded as a distinct contraindication to transfusion.

THEORETICAL AND PRACTICAL CONSIDERATIONS  
CONCERNING THE SIGNIFICANCE OF THE CON-  
JUNCTIVAL REACTION (OPHTHALMO-  
TUBERCULIN TEST).\*

A. WOLFF-EISNER, M. D.

The new tuberculin reactions have opened up a wide field in connection with both theory and practice and have revived the discussion of many questions that had come to a standstill. I do not regard it as my task this evening to take up all of the theoretical questions; and the lack of time would preclude this. I shall occasionally refer to the papers in which those interested may find future data that may interest them. I believe it would be best to pick out a few practical questions and try to come to a conclusion concerning them.

Recently a number of new tuberculin reactions have been placed at our disposal for the diagnosis of tuberculosis. A large amount of literature has followed the first publication about these matters, a great part of which is worthless because of an insufficient knowledge of the fundamental basis of the reactions on the part of the observers. A recital of such examples is not in place. Such publications have caused confusion and dispute, a fact which has made the practitioner avoid this field of contest. But the time of toil and trouble will pass. It was the unavoidable result of an unsubstantiated approval of methods, from which I kept aloof, as is shown in my first communication on the subject. We have now first the old subcutaneous method of Koch; second, "the Stichreaction," though just as old, newly applied; third, the "cutaneous" and the conjunctival reaction; fourth, a series of so-called new reactions which I will not discuss.

The subcutaneous reaction is a specific one; it is a very sensitive test. A positive result indicates the presence of tuber-

\*Read by invitation at the meeting of the New York Pathological Society on October 14, 1908.

culosis, but does not demonstrate necessarily an active or clinically evident tuberculosis. The occurrence of a positive reaction in 50 to 80 per cent. of clinically healthy individuals tested by the subcutaneous method should guard against such an error. I would not mention such a self-evident fact before this assemblage were it not that such errors are made daily in practice and stated in literature.

On the whole, the cutaneous and the "Stichreaction" give the same results as the subcutaneous method, which fact establishes their importance for clinical purposes. They are simple, safe methods which can be substituted for the subcutaneous method, demonstrating the same facts. They demonstrate a tuberculous focus which, however, may be inactive or latent.

The conjunctival reaction differs materially from the "cutaneous" and the Stichreaction, being a reaction on a mucous membrane. It is positive in active tuberculous processes which are not too far advanced and does not react in those cases in which a clinical examination is negative. It has already been shown that some of the apparently healthy people who gave the reaction had active tuberculosis. The future will tell whether or not tuberculosis is present in the remaining 5 to 8 per cent. But we can say to-day that, in contradistinction to the other tuberculin reactions, the conjunctival reaction is the one which indicates an active tuberculosis. An apparently healthy individual showing a positive conjunctival reaction is to be regarded in a suspicious light as being afflicted with an active tuberculosis.

These facts are proven by the records of reaction in 4,000 cases obtained under all precautions. The diagnostic value can only be found in the positive reaction. I have never stated that the negative conjunctival reaction excludes the presence of active tuberculosis, but it is improbable, excepting in cases in which clinically an active tuberculosis is present. For this reason the conjunctival reaction has a greater diagnostic value than the subcutaneous reaction. At first we considered them of equal value, but comparative examinations in about 100 cases have

convinced us of the greater clinical value of the conjunctival reaction.

The inherent difference between the tuberculin local reaction and the subcutaneous method lies in the production of a typical tuberculin reaction far from the seat of the existing disease, that is, the avoidance of lighting up a fresh process at the seat of the original lesion. The rise of temperature in the subcutaneous method is not the element of danger, but the starting up of activity at the seat of the old lesion is the serious consequence; a process, the progress of which can not be limited. In the recognition of this specific advantage of the conjunctival reaction, the contraindications become evident, which I have adhered to from the beginning, having neglected them only once, in consequence of an error. In a paper read before the Berlin Ophthalmological Society, December, 1907. I stated the contraindications. This was before the time when unfortunate experiences proved the correctness of my theoretical deductions. The prevention of reaction in the primary focus of the disease is the cardinal point.

Therefore, the conjunctival reaction is contraindicated if the eyes are or have been the seat of tuberculous disease, or even if there is a suspicion of the existence of such a lesion in the eye. Again application of the conjunctival reaction in an eye which has reacted is inadmissible and useless because it would bring about a reaction at what is practically a tuberculous focus. This would not have any diagnostic value. It would act just as a cutaneous reaction indicating a process which may have been latent. Another contraindication lies in the use of too concentrated preparations, especially the so-called "test" preparations. Their harmfulness especially appears when, as sometimes occurs, the conjunctival reaction is contraindicated for one of the reasons given above.

I recommend for use for the conjunctival reaction the "Ruete-Enoch<sup>†</sup> Tuberculin for Ophthamo-reaction" in 1 to 2

<sup>†</sup>Made in Hamburg.

per cent. solution, the efficacy and safety of which I have tested; as to its activity I can vouch. With more concentrated solutions better statistics can be obtained, because in persons with active tuberculosis a higher per cent. of positive results will be produced. But I consider such statistics valueless, because they enforce a reaction in cases which are clinically evident, and in incipient cases my method gives such distinct signs that it is unnecessary to deviate from a harmless form of reaction.

In cases of tuberculosis in the early stages, the reaction used according to my directions give such distinct signs that no reason exists to vary my form of using the reaction, so often proved to be absolutely harmless. (A negative result of conjunctival reaction, in using the solutions I suggest, gives important prognostic evidence which is not to be obtained by the use of other concentrations.)

I admit freely that the ophthalmologists are competent to judge the value of the conjunctival reaction, but they must recognize the above mentioned contraindications and must get their experience from general medical cases. I am sorry to say that the ophthalmologists have hardly ever studied the contraindications, in consequence of which the conjunctival reaction will become prominent, only after overcoming many prejudices founded on ophthalmological publications.\* It is not a mere coincidence that the ophthalmic clinic of Silex obtained very favorable results by using the method exactly according to my directions (tests made by Erlanger).

We have already said that the conjunctival reaction can be employed in diagnosis in internal medicine. But you will hear occasionally that the reaction is quite uncertain because it may be negative in tuberculous patients and positive in clinically healthy persons. This only confirms my statement and shows the clinical inexperience of the observer, because he does not appreciate that these negative reactions may be found in consumptives and that healthy people, who give positive conjunctival

\**Wiener Klinischer Wochenschrift*, 1908, No. 33.



reactions should be regarded with ten times as much suspicion as those who react positively to a subcutaneous injection of tuberculin. And you know that many clinicians consider even such a subcutaneous reaction as quite important from a diagnostic standpoint.

Mistakes are also made concerning my opinion that there is a prognostic value to the reaction. Nevertheless, I can state that this so seriously opposed opinion is coming slowly but surely to the front. Therefore, I am anxious to correct mistakes in literature. I declared that a negative conjunctival reaction is to be taken as evidence of unfavorable prognosis in manifestly tuberculous individuals (where bacilli are found), but I never said that a positive reaction indicates a favorable prognosis. Furthermore, I never stated that a negative conjunctival reaction occurring with a positive subcutaneous one indicated an unfavorable prognosis. In such cases I decide on a latent tuberculosis, while Ropke<sup>†</sup> actually states that I believe the opposite. This can be satisfactorily explained by the fact that Ropke and I differ in the interpretation of what constitutes an active tuberculosis.

The prognostic conclusions of Teichmann and myself \* are based upon the course which the cutaneous reaction pursues. I wish it clearly understood that the prognostic deductions pointed out from the first by me have at least as great importance as the diagnostic ones, and have not been changed in any important features. This prognostic application is the reason why I practice both the cutaneous and the conjunctival reaction at the same time.

There is not, as may seem, anything mystical about making the prognosis depend upon the course of the reaction. Let us consider a continued reaction (Dauerreaction) which indicates, according to my conclusions, a cure or a favorable course. Such a reaction indicates that at the point of reaction the tuberculous

<sup>†</sup> *Brauer, Klinik der Tuberkulose, Bd. 9, Heft 3.*

\* *Berliner Klin. Wochenschrift, 1908, No. 2.*

poison causes a connective tissue formation. It is only necessary to suppose that the seat of disease reacts or has reacted in the same manner through the incorporation of these poisons, and then the result obtained by the continued reaction is easily understood. It is not to be wondered at if empirical observations have led to the same conclusions.

Here we find a strictly logical state of facts whose correlations are not at first recognizable. Wolfson and myself have made a great number of opsonic examinations, and we arrived at the conclusion that this trying procedure gives no better diagnostic results than an exact clinical examination in combination with the use of local reactions. The control of a tuberculin treatment by the determination of the opsonic index is another matter.

We supposed that we would find a high opsonic index in cases of strong tuberculin reactions, and particularly in cases showing a "Dauerreaction." This was not at all the case and it only gradually developed why this was so. A high opsonic index is produced by absorption of tuberculous poison from the focus of disease. This is prevented by the formation of connective tissue, which explains, therefore, the absence of a high opsonic index.

These opsonic experiments, together with our experiments concerning the binding of complements in tuberculous subjects,\* prove that the poisons from the tubercle bacilli are absorbed, being identical in their effect with tuberculin. This fact is of great fundamental importance because it explains the difference in the opinions of many observers which could not otherwise be explained. It is well known that to-day there are adherents and opponents to the tuberculin treatment, from both a diagnostic and a therapeutic standpoint, the one side continuously reporting injurious effects which have not been observed by the other.

The above mentioned facts demonstrate that when a patient is injected with tuberculin, the same process takes place in him

\**Wiener Klin. Wochenschrift*, 1908, No. 37.

which would develop eventually as the result of absorption of tuberculin from his own tuberculous lesions. Under these circumstances, it is dependent upon the point of view of the observer whether he holds the tuberculin injection or the disease itself accountable for the result. The same fact explains, it seems, what is apparently paradoxical, that the statistics of the adherents of tuberculin do not differ greatly from those of its opponents. I wish to state, *en passant*, that no good basis exists for the compilation of statistics of pulmonary disease. I shall discuss this on another occasion.

Inasmuch as in all tuberculous subjects tuberculin appears in the circulation, it can be easily understood that the results with or without tuberculin treatment can not differ very materially. It remains for the future to determine which individuals will require a tuberculin treatment. The observation of the local reaction, the study of the opsonins and the clinical course of the illness will be the determining factors.

Numerous experiments, the observation of local reactions and the work of others have convinced me, that there is a certain immunity in tuberculosis, an immunity against poisons which have become soluble and another against the bacilli themselves. The latter is most likely a bacteriolytic one. The immunity against poisonous matter, freed by lysis, is not an antitoxic one, but corresponds to the mechanism of the natural immunity against toxins which I have recently described.

The toxin immunity of the naturally non-susceptible animal consists of the binding of the poison by organ receptors (this stands in contrast to active immunity of an animal originally susceptible). If endotoxins are bound as described above for natural immunity, the fixation seems often to occur by means of the receptors in connective tissue.

Two cases will illustrate this: The cutaneous reaction was applied to both. They then received 1, 3, 5 mg. of tuberculin by subcutaneous injection and reacted with increasing fever. Using 7 and 9 mg., the general reaction did not occur, but in place of it an intense inflammation of the old cutaneous reaction appeared

(in one case erysipelas, and in the other an intense furuncle). These phenomena have been constantly produced by me in cattle. Their interpretation involves great difficulty and is only possible for those who have had an experimental training in the fundamental work of natural immunity against toxins. The tuberculin which has probably been made absorbable by lytic processes, is carried to those points where the receptors are located. These are essentially the foci of disease, but other places can act as foci with receptors. If all the tuberculin is bound here, a tuberculin injection will cause a local reaction. If it is only partially bound there will be a weakened or delayed local reaction and a late general reaction. We are thus enabled to protect the general organism from the influence of the tuberculin poisons by directing their action to less vital tissues, as, for instance, connective tissue, and we will probably be enabled to make therapeutic use of this fact. Taking it for granted that the protection of such receptors in the connective tissue will be of most advantage, and considering the numerous observations made by Hollender, Joseph, *et al*, that certain forms of skin tuberculosis preclude tuberculosis of the lungs, we can understand that after an injection of tuberculin the local reaction can appear before the general reaction, or even that the general reaction that is to be expected does not appear at all or is favorably influenced in its progress.\*

For some time past I have been enabled by intracutaneous injections of small doses of tuberculin, or through the inunction of tuberculin ointment, to obtain in patients with lung disease artificial skin foci. In the second edition of my "Ophthalmodiagnose" it is my intention to give more accurate reports of the fundamental principles involved in this therapeutic measure, but I will not allow myself to be misled in reporting successful results too soon.

It can be easily seen how in this field purely theoretical with practical results are most intimately connected, of which

\*Cf. Ophthalmodiagnose, Wolff-Eisner, Wuerzburg, 1908.

the conjunctival reaction, the initial step in our observations, is the most palpable proof.

I should like to call the attention of veterinarians to the fact that the application of the conjunctival method in cattle presented points of extreme difficulty. However, in the experiments that I have made with the aid of the agricultural department the principal difficulties have been overcome. It is to be hoped, therefore, that in the veterinary practice the conjunctival reaction will be developed in as exact a degree as in the human species.

In conclusion let me give a summary of my remarks:

1. The subcutaneous and the cutaneous methods are specific reactions for tuberculosis. As they both demonstrate latent tuberculosis, their use is extremely limited for clinical diagnosis.

2. The positive conjunctival reaction shows active tuberculosis.

3. The conjunctival reaction in clinically healthy individuals makes it particularly suspicious that they are affected.

4. A negative result in those manifestly tuberculous justifies a bad prognosis.

5. In advancing tuberculous disease negative reactions become more frequent.

6. A positive conjunctival reaction does not justify a good prognosis, but this is the case only in the so-called cutaneous "Dauerreaction," (continued reaction).

7. It is possible to create receptors in tissues that are indifferent as regards life such as connective tissue, these receptors attracting tuberculin and localizing the toxic action. This observation is of therapeutic value.

#### *Closing Remarks.*

DR. WOLFF-EISNER: Let me first thank Dr. Richard Wiener for translating my paper into English, and Dr. Libman for reading the same.



In my communication I could not give all the investigations concerning the theory of the action of tuberculin, especially the lytic theory of the tuberculin reaction. You can find the facts given in the first edition of my book, which was published in New York by Wood & Company about the 10th of October; new facts you will find in the *Berliner klinische Wochenschrift*, 1908. The second German edition of my book will soon be published. I hope you will enter upon the discussion of my paper without considering me a guest.

When I read my paper at the meeting of the German Medical Society last week, the chairman pointed out that the name "ophthalmoreaction" is a misnomer for several reasons. At the same time he stated my absolute priority. At the same meeting he said that I came to America to stand up for my rights. This was not my intention, because I thought there was no necessity, but yesterday while in the library of the Rockefeller Institute reading about one hundred papers of the American literature concerning the matter, I found only Calmette mentioned. I claim that I communicated the conjunctival reaction and discussion of the first paper of von Pirquet on the 15th of May, 1907, while Calmette made his communication to the Academy of Sciences in Paris, June 16th. To Calmette belongs the credit of having greatly assisted in having the reaction quickly adopted by the profession.

There can be no question about these facts; Calmette himself points out that the paper of von Pirquet was the cause of his investigations and this paper already contains my communication about the discovery of the conjunctival reaction. It is not generally known that on the same day on which Calmette read his paper, Vallee also read a paper concerning the conjunctival reaction in cattle, in which he stated that his investigations were undertaken in connection with my discovery.

Of greater importance to me than the question of the priority of the discovery of the reaction, is the part I took in building up the scientific structure which is based upon it, and its application for the prevention of tuberculosis. I should be

only too glad to work harmoniously with all those who have some aim.

There is no difficulty in applying the reaction, but the matter is not as simple as it may appear. It took my collaborators several months before they were able to carry out my intentions. In cases in which there is a contradictory result with the reaction, it is absolutely necessary to compare the results with the findings of the physical examinations if you want to avoid a wrong interpretation. If you can not exclude apparent contradictions, I would like to have you bring the matter before me. Many a physician has come to me with a very critical point of view, but no one has left me unconvinced.

#### *Discussion.*

DR. PAUL COURMONT, Lyons, France: Dr. Wolff-Eisner's communication gives me the opportunity of saying a few words concerning the comparative value of the different diagnostic methods in testing for tuberculosis in which tuberculin is employed, and the so-called sero-diagnosis and sero-prognosis by means of agglutination. For the past ten years Dr. Arloing and myself have employed in Lyons, the sero-diagnostic method in cases of tuberculosis. This consists in making agglutination tests with the serum of tuberculous patients and the tubercle bacilli grown in homogenous cultures. This method has always given us excellent results, just as it has done in the hands of other investigators in Germany, Italy, and Sweden. It is easy to grow the tubercle bacillus in homogeneous cultures and to send such cultures from place to place for agglutination tests. We have sent from Lyons a number of cultures of our *Bacillus* "A" to different countries. The agglutination test is done in the same manner as in cases of typhoid fever. Only a few drops of serum are necessary for the test, and these may be obtained by pricking the tip of the finger or the lobe of the ear. If one compares this method with those in which tuberculin is employed (be it under the skin or in the eye) one sees that all these give similar results; but there are many advantages in favor of the sero-diagnostic

method. With all the methods the reaction is positive in a large number of cases of tuberculosis, and negative in very severe forms of the disease. With these three methods the reactions are positive in a sufficiently large number of subjects who are apparently in good health or in whom there are no clinical manifestations of tuberculosis. It is even more remarkable that the results obtained in non-tuberculous hospital patients are the same with the subcutaneous tuberculin method as with the agglutination test. About forty per cent. of such cases give positive results with the agglutination tests whereas forty-six per cent. are positive with the subcutaneous tuberculin test according to the statistics of 3,000 cases collected by Dr. Beck. This agreement of results shows that the two methods are equally good to indicate latent tuberculosis. In any event, if one should raise the objection to this method as being too sensitive and indicating the presence of tuberculosis where no other manifestations are present, then the same objection must be raised to the other methods used in the diagnosis of these cases. On the other hand the advantages of the agglutination test are the following:

First, The harmlessness of the method. The only operation which it is necessary to do upon the patient for this test is to obtain a few drops of blood from the tip of the finger—a procedure which is absolutely without danger. One can not say as much for the tuberculin tests. The injection of tuberculin under the skin can give general systemic reactions at times very annoying so that there is always required a certain amount of discretion in its use. The ophthalmo-reaction is subject to mishaps. In Lyons there have been observed a number of cases of severe keratitis. We have ourselves had one such case and several cases of severe conjunctivitis which lasted a number of days and gave rise to severe headaches. In a number of instances the patients have protested violently against the results of the reaction. The ophthalmo-reaction then has a number of objectionable features. One, perhaps, would say that these accidents are rarely found in a number of cases published, but it is sufficient that these accidents do happen: especially in view

of the fact that there are other methods of testing which are innocuous.

Second, Ease and rapidity of the test: A few drops of blood (one c. c. or thereabouts) are sufficient for the reaction. The test can be done in the laboratory away from the patient. After the blood is obtained the patient does not require any further observation on the part of the one performing the test. This, of course, is impossible with either the subcutaneous or ophthalmo-tuberculin tests.

Third, With the ophthalmo-reaction the patient can, in a way, tell whether or not the reaction is positive, which, of course, is a pernicious fact for those who may be affected by this knowledge. This, however, is not the case with the agglutination test.

Fourth, The possibility of making a local diagnostic test: We call this the local sero-diagnostic test, because the agglutination test may be made with the few drops of serum obtained from serous effusions, especially in cases of pleurisy. The reaction thus obtained gives proof of the localization of a tuberculous lesion. We have statistics of 120 cases of tuberculous pleurisy so examined. It is evident enough that such a local diagnostic test is impossible with tuberculin which gives only general proof of a tuberculous infection.

Fifth, Sero-prognosis by study of the variations in agglutination: The ophthalmo-test presents different degrees of reaction amongst different subjects, but these variations do not stand in close relations to the prognosis. The absence of an ophthalmo-reaction alone, in a tuberculous patient, seems to be a bad prognostic indication; the same is also true with the serum reactions. Furthermore, the variations in the agglutinating power of the serum of tuberculous patients are very interesting clinically. We have shown that agglutinating power rises when the patient makes good progress towards recovery and falls, on the other hand, when the case becomes more severe; agglutination at times disappears entirely in the period preceding death. One can draw very important con-



clusions in the study of the agglutinating power of tuberculous sera and their variations. We have shown by statistics of 112 cases of tuberculous pleurisy followed up for eight years that the pleuritics whose effusions (sero-fibrinous) agglutinated, recovered in 79 per cent. of the cases, whereas those whose effusions did not agglutinate, died in 73 per cent. of the cases.\* It is therefore necessary to study the variations in agglutinating power of blood and serous effusions of tuberculous patients. Similar studies did not seem possible with the ophthalmo-reaction and it is also unwise to repeat the ophthalmo-tests in the same patient; and, furthermore, several inoculations of the conjunctiva with tuberculin seem to sensitize and give false results. It is therefore certain that all the advantages are in favor of the agglutination test.

In conclusion, I would insist upon making diagnostic reactions in the manner described. One is often wrong in asking whether agglutination and tuberculin reactions have absolute diagnostic value. There is no sign in medicine which is absolute or incontrovertible. The diagnosis and prognosis can be given only by assembling the different signs and not by selecting any one sign from all those present. The reactions of which I have spoken have by themselves only a relative value. They must be supported by clinical evidence in order that we may ascribe to them their full value. One should never rely upon these tests in the absence of all clinical evidence.\*

DR. WOLFF-EISNER: I agree with Dr. Courmont that one should use as many methods as possible; I have always asked that this be done. He is right when he says that the conjunctival reaction does not allow titration. If this is possible with the agglutination reaction it would be a great gain even if only for the reason that one could do without the inexact and time-robbing

\*See P. Courmont: Sero-prognosis in Cases of Pleurisy, *Journal of the American Medical Association*, May 19, 1906.

\*See P. Courmont: The Agglutinating Power in Tuberculous Patients. Sero-diagnosis and sero-prognosis: International Congress for Tuberculosis, Washington, 1908.



opsonic technic which I have been using to estimate the degree of immunity.

The opsonins really seem to go hand in hand with the agglutination, but the estimation of the agglutination was almost entirely dropped for this purpose. I would be very glad if Dr. Courmont would succeed in so developing the method that it would be a valuable addition to the conjunctival method. The findings of Dr. Courmont in typhoid and rheumatism, are absolutely opposed to my results. I have not found the conjunctival reaction present in the course of the study of very much material; for instance, in one hundred typhoid cases, I found the reaction only twice and in one of the two cases I later found tubercle bacilli.

## A CASE OF TYPHOID FEVER ASSOCIATED WITH CHOLELITHIASIS, CHRONIC SUPPURATIVE CHOLECYSTITIS AND HEPATIC ABSCESSSES.\*

BY ROBERT J. CARLISLE, ASSISTANT VISITING PHYSICIAN, BELLEVUE HOSPITAL AND D. C. MARTIN, M. D., VOLUNTARY  
ASSISTANT PATHOLOGIST.

*(From the Pathological Laboratory of Bellevue Hospital)*

DIRECTOR: CHARLES NORRIS, M.D.

Since the original publication in 1890 of Gilbert and Girode's article dealing with the occurrence of the typhoid bacillus in a case of suppurative cholecystitis, an abundant literature has accumulated, proving the frequent association of the typhoid bacillus with lesions of the biliary tract. As a result of the large number of casuistic contributions to this subject, it has been firmly established (1) that, during the course of a general typhoid in-

\* Presented by Dr. Martin at the October meeting of the New York Pathological Society, 1908.

fection, the typhoid bacillus regularly finds its way into the gall-bladder and is excreted with the bile; (2) that it may remain latent in the gall-bladder for an indefinite period of time without causing local lesions; (3) that typhoid bacilli persisting in the gall-bladder may be discharged into the intestine with the bile, and that such persons may, in this way, become "typhoid carriers" or distributors; (4) that the typhoid bacilli, instead of remaining as innocuous parasites in the gall-bladder, may form the nucleus for the development of calculi, or may cause a catarrhal or suppurative cholecystitis, with or without an infection of the biliary ducts; such an inflammation may occur in the course of a typhoid fever, or at any subsequent time; (5) that rarely, in the absence of any antecedent history of general typhoid infection, typhoid bacilli may cause "primary" lesions of the biliary tract. Such cases have been reported by Cushing<sup>2</sup>, Wilson<sup>3</sup>, Richardson<sup>4</sup>, Guarnieri<sup>5</sup>, Stewart<sup>6</sup>, Burlew<sup>7</sup>, Pratt<sup>8</sup>, Bluementhal<sup>9</sup>, Forster and Kayser<sup>10</sup>, and others. Although the objection may always be advanced, that there may have been a previous mild attack of typhoid fever unnoticed or forgotten by the patient, the number of cases seems so great that it is pushing skepticism too far to deny the occasional primary localization of the typhoid bacilli in the gall-bladder.

The case here reported, though difficult of interpretation in some regards, is sufficiently interesting to merit consideration.

The patient, Jane S., was admitted to Bellevue Hospital on August 17, 1908, in the service of Drs. Le Fevre and Carlisle.

Family history negative.

Previous history. Had cholera morbus when a child, and "influenza" some years previous to present illness. One and a half years ago she was admitted to Bellevue Hospital.

The case on admission to the hospital was looked upon as one of acute lobar pneumonia, and acute gastro-duodenitis of alcoholic origin. After two or three days' observation and a closer investigation of the previous history, the jaundice and local abdominal signs, cholelithiasis was diagnosticated and the possibility of the correct diagnosis being typhoid fever then pre-

sented itself. The Widal reaction was returned as positive on the third day after admission, and a blood culture, taken on the second day following, confirmed the diagnosis by the presence of the typhoid bacilli in pure growth. The essential points in the history follow :

Jane S., aged 25 years, a housewife by occupation and the mother of two children, was admitted to Bellevue Hospital to the service of Dr. Egbert Le Fevre on August 17, 1908, at 1 p. m. with a temperature of  $105^{\circ}$  F., pulse 120, resp. 28. She had been sick nine days with dry cough, pain in the left side of the chest, vomiting and epigastric pain. She had been treated at a dispensary for dry pleurisy, had been drinking immoderately to dull the pain and distress. She had been jaundiced for five days and stools were alcoholic.

Past illnesses: Cholera morbus when a child, and influenza (?) some years ago. In February, 1907, was treated in Bellevue Hospital for gastro-enteritis. This attack was accompanied by severe pains in the epigastrium which radiated to the back, tenderness and vomiting. Though she has had similar attacks at various times since, she has never had jaundice before. These attacks were accompanied by dull aching pains in "stomach."

Present illness: Began in a manner similar to the previous attacks, but the symptoms of pleurisy soon developed. Had shortness of breath, dry cough and severe pain. Had no nose-bleed and no headache, no diarrhoea, no chill, no marked paroxysmal pain. Vomiting ceased two days before admission.

Physical examination: Medium sized, well developed, stout and somewhat anaemic, with marked icterus.

Lungs show consolidation of upper right lobe, with a few crepitant rales; dry pleurisy on left side at the base and slight general bronchitis.

Abdominal walls are thick with fat, soft, distended by tympanites. Tenderness in epigastric region and over gall-bladder area. No tumor.

Liver is easily palpated 3 inches below costal margin; edge smooth, tender.

Spleen, because of fullness in that region, is not palpable. Skin shows icteric hue; no roseola.

The patient's temperature ran a continuous course between  $102^{\circ}$  and  $105^{\circ}$  for three days, and then continuously between  $102^{\circ}$  and  $104^{\circ}$  for a week longer, dropping rapidly to normal on August 28, the twenty-first day of the disease; varied between  $100^{\circ}$  and  $101^{\circ}$  on the twenty-second day, when after a second drop to normal, it steadily rose, again reaching a point above  $104^{\circ}$  on the twenty-fifth day of the disease; became more remittent ( $101^{\circ}$ - $104^{\circ}$ ) till death on the twenty-ninth day (September 5). The pulse was rapid, feeble and dicrotic, ranging between 110 and 136 and later as high as 140-150. Respirations were rapid most of the time, 35-45-48. Lungs, upper left lobe, presented signs of consolidation on second day following admission. Distinct signs of resolution in both upper lobes were found on August 25. General bronchitis became more marked, numerous small and large rales and subcrepitant rales being heard over both lower lobes.

The patient complained frequently of severe pain in left lower axillary region and on August 26, nine days after admission, of stabbing pains in right hypochondriac region. Examination of the gall-bladder area was always difficult on account of the abdominal distension, but a distinct rounded mass was felt apparently connected with the liver. Palpation of this tumor caused great pain. Ice bags gave some relief. Spleen was indistinctly palpable this day.

On August 29, the patient complained of considerable deafness, but no pain in either ear. On September 3, the left ear drum perforated and on the following day the right. A sero-purulent discharge came from both ears.

The patient's general condition which was bad from the first, became very serious on August 31, and remained so until the end.

The blood examination showed a leucocytosis of between 13,000 and 35,000. The polymorphonuclear cells were relatively and absolutely increased (83-93%). The urine contained a

trace of albumin, bile and some hyalin and few granular casts. Diazo reaction positive.

Death took place on the twenty-ninth day of the typhoid fever. The jaundice remained, varying slightly in intensity on several days. There were no chills.

From the records of the necropsy performed by Dr. Pappenheimer, twenty-eight hours after death, the following notes may be abstracted:

Body is that of a quite well nourished female, apparent age thirty years. Skin and conjunctivae show a marked bright yellow icterus, and there is icteric staining of all body tissues and fluids. Panniculus is abundant. Musculature well developed but pale. On opening the peritoneal cavity there is found a small amount of somewhat sticky sero-fibrinous exudate in the dependent portions. A few fibrin threads are present on the visceral serosa.

Liver projects a hand's breadth below the ribs in the median line, and there are fresh fibrinous adhesions between the anterior surface and the diaphragm. The omentum is adherent both to the lower pole of the spleen and in the region of the pylorus and gall-bladder, where it forms a thickened, firmly adherent mass. The lower pole of the spleen reaches to the costal margin. The pleural cavities are free from fluid. Lungs are adherent to the diaphragm by a small amount of fresh fibrin.

Heart relatively normal in size. Right auricle is filled with yellow clot. Valves and orifices are normal. Musculature is strikingly moist, pale and flaccid. There are a few minute sub-endocardial petechiae. The aorta is delicate and free from atheroma throughout.

Lungs show fibrinous pleurisy, lobular pneumonia and bronchitis.

Liver weighs 2745 grams, and is enlarged in all dimensions. The surface, especially of the left lobe, is covered with a fine deposit of recent fibrin, and there a number of yellowish-green, raised prominences on the surfaces of all lobes, which on section correspond to collections of greenish pus. On section the left lobe of the liver is riddled with suppurative foci, which on



closer examination shows a central yellowish core, surrounded by a greenish zone, corresponding in the gross everywhere to the small bile passages. The right lobe shows a smaller number of similar foci. On opening the duodenum, a thick, golden-yellow fluid, mixed with considerable detritus, exudes from the papilla, without exerting pressure on the gall-bladder. A probe passed into the duct from the duodenum enters the gall-bladder, and hepatic ducts without difficulty. The common duct, upon being split open, is found filled with thick, yellowish detritus, is everywhere widely patent, and contains no calculi.

Liver, stomach and duodenum were removed *en masse*, and an attempt made to dissect out gall-bladder and ducts.

The gall-bladder is buried in a mass of adhesions. The cavity is filled with the same thick, yellowish-brown material as the common duct, and shows a number of sacculated diverticula, containing smooth, non-faceted calculi, varying in size, the largest about the size of a cherry-pit. The precise relationship of the cystic and hepatic ducts to the gall-bladder cannot be made out; some of the calculi appear to be in the branches of the hepatic ducts. In all, there are about a dozen stones. On splitting up the intra-hepatic portion of the cava, there is found at the point of entrance of the left hepatic vein, a small thrombotic mass, about the size of a pea, and an underlying focus of suppuration in the vein and adjacent tissue. The portal vein is free from thrombus, and appears normal.

The spleen is slightly enlarged. The pharynx, larynx and trachea are normal. The stomach is normal. The small and large intestines are normal throughout, save that the mucous membranes are somewhat paler than normal. The Peyer's plaques and solitary follicles are not macroscopically visible, except by transmitted light. The intestinal contents consist of a small amount of unformed, bile-stained fecal material.

The lymph-nodes are very small, pale—without gross areas of necrosis.

The uterus, tubes and ovaries are practically normal. The kidneys show lesions of parenchymatous degeneration. The ad-

renals and bladder are normal. The brain is normal. Both middle ears are filled with greenish pus. The sphenoidal sinus also contains purulent exudate.

*Anatomical Diagnosis:*—Typhoid Fever; Suppurative Cholecystitis and Cholangitis; Cholelithiasis; Lobular Pneumonia; Fibrinous Pleurisy, Acute Bronchitis; Acute Sero-fibrinous Peritonitis; Suppurative Otitis Media, (Double).

*Bacteriological Examination:*—*B. typhosus* was twice isolated from the blood during life. Smears from the liver at autopsy showed numerous Gram-negative bacilli and a few Gram-positive, lancet-shaped, indefinitely encapsulated diplococci. Cultures were made from the peritoneum, liver, gall-stones, spleen and middle ear.

The gall-stones were carefully washed in 1:1000 bichloride and sterile water, and then washed in sterile Petri dish with broth, and plated on agar. Streak plates on ascitic agar were also made from the liver, in an attempt to isolate the diplococci. This was unsuccessful, plates being overgrown by the typhoid bacillus.

From the peritoneum, liver, spleen, gall-stones and ear, a motile Gram negative bacillus, giving all the cultural and fermentative reactions of the *Bacillus typhosus* was obtained, practically in pure culture. Positive agglutinations were also obtained with an immune rabbit serum of known titer.

*Histological Findings:*—Liver. Sections were taken for examination from various portions of the liver, and stained by the usual methods. The essential and most striking lesions found are widespread and irregular areas of necrosis, to which are added the evidences of an acute inflammatory reaction.

Taking for description such a necrotic area, we find a central bile-stained core, surrounded by a broad zone of disintegrating liver cells in every stage of necrosis. In many cases, such an area is sharply circumscribed and the adjacent liver lobules, though tangentially compressed, are well preserved. In other cases, the necrotic area is walled in by a broad zone of leucocytic infiltration. This is especially the case about the larger areas,

where it may be so extensive as to give them the character of abscesses. Bacteria (bacilli and cocci) may or may not be present in the necrotic areas; where found, they are situated principally in the central portions of the necrotic foci.

Striking changes are found also in the liver capillaries. Whereas the portal radicles and the hepatic arteries are distended with well-stained red blood cells, the capillaries themselves contain remarkably few well preserved red blood corpuscles. Instead, they are dilated and more or less filled with granular and hyalin detritus, and large cellular elements, which in many cases are attached to the capillary wall and may be definitely identified as swollen endothelial cells, or as dislodged parenchymal cells which have found their way into the capillaries as a result of the extensive destruction of the liver substance. Polynuclear leucocytes are found rarely; small round cells with intensely staining nuclei are more abundant.

In general, there is little increase in the interstitial tissue of the organ. In some regions, however, the periportal connective tissue is distinctly more abundant than normal, and evidence of recent proliferation is afforded by the presence of lymphoid and plasma cells and fibroblasts in considerable numbers. In the neighborhood of the necrotic areas, the periportal connective tissue frequently presents an edematous appearance.

The central veins are found in some sections filled with a structureless hyalin material, staining faintly blue with hematoxylin. The liver cells in the ventral portion of the lobules contain considerable bile-pigment, those of the peripheral portions often show a moderate grade of fatty infiltration.

The biliary ducts and the portal vessels, even those in close proximity to the necrotic areas, are absolutely normal. The significance of this unexpected finding we shall consider later.

The histological findings in the remaining organs may be passed over with a word. In the spleen, were found a few small areas of focal necrosis. In polychrome methylene blue preparations, a few short bacilli were found. Plasma cells were very abundant, many having two or three nuclei.

In the lungs, there is present an acute bronchitis and peribronchitis, with relatively large numbers of lymphoid and plasma cells in the exudate.

In summarizing the features of this case, we should like to emphasize the following points: The absence of any definite history of previous typhoid infection; the presence of vague symptoms of over a year's standing, referable to gall-stone disease; the sudden onset of an acute febrile disease, with icterus and other symptoms pointing to lesions of the gall-bladder and liver, and a complicating lobar pneumonia; the typhoid septicaemia. At the autopsy, we find a chronic cholecystitis with calculi, irregular necroses and abscesses in the liver, and as a result of the bacteriological examination, evidence of a generalized and local infection with the typhoid bacillus. On analyzing this case, especially as regards the sequence of the various lesions, we meet with various problems. The important question as to whether the typhoid cholecystitis was a primary infection, or the sequel of an unrecognized typhoid infection at some previous time, it is impossible definitely to decide. Possibly the illness described as influenza may in reality have been a mild typhoid. Details are wanting, but that the typhoid cholecystitis was of long standing, is evident from the character of the lesions. The lesions in the liver are especially difficult to interpret. The study of the sections seems to indicate that the essential histological feature is a necrosis of the liver cells, and that the inflammatory changes observed about some of these areas are of secondary importance. The marked lesions found in the capillary endothelium would perhaps suggest a primary toxic influence as a principal factor in the causation of the lesions. Although occasional organized parietal thrombi were found in some of the branches of the portal veins, and more recent hyalin thrombi in some of the hepatic veins, it seems hardly warranted to ascribe the wide-spread liver necrosis to these factors, particularly as there is no affection of the larger portal vessels. The biliary ducts, with few exceptions, are normal, so that there is no ground for considering the liver lesions as caused merely by an infectious cholangitis. We can



only say that in the course of a chronic typhoid infection of the gall-bladder, there developed an acute typhoid septicemia, associated with marked necrotic lesions in the liver.

Of course, it is not possible to say that the patient was a typhoid distributor, but in view of the recent German research work, and the case so well described by Soper, it certainly appears probable.

We desire to express our thanks to Dr. Alwin M. Pappenheimer for his assistance, encouragement and advice.

# REFERENCES.

1. GILBERT ET GIRODE: Contribution a l'étude bacteriologique des voies biliaries. *Comptes rendues de la Soc. de Biol.* 1890.
2. HARVEY CUSHING: Typhoidal Cholecystitis and Cholangitis. *Bull. Johns Hopkins Hosp.* 1898, p. 91.
3. O. S. WILSON: Primary Typhoid Cholecystitis and Cholangitis. *Jour. Am. Med. Assn.*, 1908, May 16, p. 1607.
4. RICHARDSON: Cholecystitis due to Typhoid Bacilli, *Boston Med. & Surg. Journ.*, 1897, Dec. 2, p. 570.
5. GUARNIERI: Contributazione alla patogenizi delle Infezione Biliari. *Rev. Gen. Ital. di Clin. Med.*, 1897.
6. STEWART: Primary Typhoidal Cystitis with Calculi. *Am. Medicine*, 1904, vol. vii, p. 1018
7. BURLEW, J. M.: Typhoid Cholecystitis with Calculi, without Evidence of Typhoid Fever. *Medicine*, Oct. 1903. (Abstracted in *Am. Med.*, 1903, vol. vi, p. 959.)
8. PRATT: Typhoid Cholecystitis with Observations upon Gallstone Formation. *Am. Journ. of Med. Sciences*, 1901, vol. 122, p. 584.
9. BLUMENTHAL, T.: *Münch. Med. Woch.*, 1904, No. 37.
10. FORSTER & KAYSER: Ueber das Vorkommen von Typhusbazillen in der Galle von Typhuskranken und Typhusbazillenträgern. *Münch. Med. Woch.*, 1905, Aug., p. 1473.
11. SOPER: Work of a Typhoid Distributor. *Jour. Am. Med. Assn.*, June 15, 1907.



## ADENOMYOMA OF THE ROUND LIGAMENT.

F. C. WOOD, M.D.

Dr. F. C. Wood presented a specimen which had been removed from the inguinal region of a patient at the German Hospital during the course of an operation for inguinal hernia. The history of the woman was of no especial interest. In the resection of the hernial sac this nodule was removed. It was a small, oval mass, about 2.5 x 1 cm., occupying part of the wall of the sac. This was cut, and in the sections there was found, besides muscle fibers and fibrous tissue of the round ligament, a number of alveoli lined by high cylindrical epithelium. There were no cilia on these epithelial cells. The alveoli were surrounded by tissue suggesting the structure of the endometrium. The morphology of these alveoli in the round ligament tumor was similar to that of the alveoli of adenomyomata of the uterus. The specimen was shown merely because it was somewhat of a pathological rarity, only about eight cases having been described.

---

## SPECIMENS FROM A CASE OF GASTRO-INTESTINAL PSEUDOLEUKEMIA.

H. L. CELLER, M. D.

The specimens demonstrated were obtained from a man, forty-eight years of age, admitted to the surgical service of Mt. Sinai Hospital in September, 1907. The clinical history may be briefly given. For about a year the patient had noticed a large, irreducible mass in the left inguinal region. The day before admission he was attacked with abdominal cramps and repeated vomiting. The bowels were moved with enemata. There was slight fever. One year previously the patient had had a similar attack that subsided spontaneously.

The patient was admitted to the hospital with the diagnosis

of acute ileus. It was noted in the physical examination that he was quite anemic and emaciated. The mass in the left inguinal region was described as being about the size of a fist, hard, not tender, not reducible. The blood count showed 10,600 white cells, seventy per cent. of which were polymorphonuclear leucocytes, thirty per cent. lymphocytes. No abnormal cells were present. Urinary findings negative.

At operation, the inguinal mass was found to consist of a packet of lymph nodes of varying size. The individual nodes could be readily distinguished in the tumor. Abdominal section revealed an intussusception at the ileo-cecal valve, and, as reduction could not be effected, the intussuscepted portion of intestine was resected. The patient's condition, which was very poor before operation, rapidly became worse, and death ensued shortly after his return to the ward.

The autopsy was performed a few hours later by Dr. E. Libman, whose report is here abstracted.

The right cervical lymph nodes are slightly enlarged. The thoracic viscera show only minor changes. There is no enlargement of the mediastinal or bronchial nodes. The liver is slightly enlarged, firm, and shows congested central veins. In every cut section there are visible one or more firm, yellow tumors, varying in size from a pinhead to one centimeter in diameter. The spleen is very slightly enlarged; lymphoid follicles prominent. With the exception of the stomach and intestines the remaining abdominal organs are negative.

*Stomach:*—Thickly studding the mucous membrane of this viscus are circular or oval elevations which vary from one millimeter to one centimeter in diameter, yellowish-white or pink in color, almost diffuent in consistency. The larger masses project into the cavity of the organ as sessile polypi. The smaller ones form flattened, frequently coalescing infiltrations immediately beneath the mucosa which is apparently thinned out over them. Toward the pylorus the walls are considerably thickened. These changes are most marked on the anterior and

posterior walls of the stomach; the pyloric antrum is entirely free from evident lymphoid tissue.

*Duodenum*:—The upper six centimeters show marked hyperplasia of the lymphoid tissue in the form of large polypoid masses elevated one-half centimeter above the mucous surface, and presenting free, overhanging edges. In color and consistency these masses are identical with those already described in the stomach. The lesion ends abruptly, leaving the remainder of the somewhat dilated and congested duodenum free.

*Intestines*:—Here the lymphoid filtrations invade for the most part the Peyer's patches, which vary very considerably in size, measuring from one and one-half to eight centimeters in length. All are pigmented, black or brown in color, of irregular outline, the larger plaques showing various stages of superficial ulceration or necrosis. They resemble the agminated patches found in the stomach in that they are composed of a number of smaller, coalescing nodules; they differ, however, in that the overlying mucosa is elevated from one-half to five millimeters above the surface of the intestine. These plateau-like tumefactions bear a close resemblance to certain types of carcinoma. The most marked changes are found in the neighborhood of the ileo-cecal valve, where fungoid masses larger than those in the duodenum are present. This is also the site of the most extensive ulceration, some of the lesions resembling those found in the early stages of typhoid. In both the large and small intestine, notably in the ascending colon, the solitary follicles also present evidences of involvement. The larger follicles are about the size of a split-pea, and resemble ordinary warts, but are softer in consistency. Some of them are hemorrhagic.

Surrounding the pancreas near its upper border, there are many enlarged, elongated, lobulated lymph nodes, soft in consistency, pink or yellow in color. The lymph nodes along the greater curvature of the stomach present similar changes.

Microscopically the gastro-intestinal infiltrations are seen to be composed almost wholly of densely packed lymphoid cells of the type usually present in these situations. These cells are

mostly confined to the submucosa, although in the larger lesions they are sometimes seen to invade the mucosa, lying between the glands. The muscular coats are nowhere infiltrated.

A similar picture is presented by the lymph nodes, where the cellular increase is so great that neither germinal centers nor sinuses can be differentiated. Irregularly scattered among the lymphoid cells are giant endothelial cells containing from one to four pale-staining, irregular nuclei. A few polynuclear eosinophiles and red blood cells are also present. Each node is sharply outlined by a slightly thickened capsule from which, in one of the largest nodes, a few narrow strands of dense fibrous tissue penetrate among the lymph cells for a short distance. There is no infiltration of the capsule, although small collections of lymphoid cells surround some of its vessels.

The enlarged Malpighian corpuscles of the spleen, as well as the yellowish areas in the liver, also contain cells of the type found in the intestinal infiltrations. In the liver the cellular masses are confined wholly to the region of the portal vessels.

Seven typical cases of lymphoid hyperplasia confined to the gastrointestinal tract are collected in a paper published by Wells (1), under the title, "Pseudoleukemia Gastro-intestinalis." To these Wells has himself added one case, while still another has been since published by Hoffman (2). Even a cursory study of the literature demonstrates that a considerable variety of conditions has been heretofore described under this head. The work of Reed, Longcope and others has established Hodgkin's disease as a distinct pathological entity. Excluding this group, the confusion that has arisen concerning the cases under discussion might be best removed by adopting the ingenious and comprehensive classification suggested by Türck. In view of the absence of blood changes as well as of evidences of malignancy, this series of cases would then fall in the category of "alymphemic lymphomatoses."

(1) *American Journal of the Medical Sciences*, November, 1904.

(2) *Archiv für Klinische Chirurgie*, 1907.

*Discussion.*

DR. W. T. LONGCOPE said that he had been very much interested in examining the specimens in this case. This type of simple hyperplasia or increase of the lymphoid cells, which Dr. Celler had described, must certainly be an unusual condition. He would like to ask whether there were any bacteriological examinations made in this case. The case was certainly not a lymphosarcoma.

DR. JAMES EWING said that he had no more definite ideas in regard to the nature of the disease than Dr. Celler had expressed. It seemed to him that it was a very important case and suggested to him transitional stages between cases which he had seen, and between which he had wondered if any relation existed. These were the so-called typical small cell lymphosarcoma, certain cases of Hodgkin's disease, and status lymphaticus. In all of these conditions it seemed to him that one had to deal with a systemic disease of the lymphatic apparatus. Lymphatic leukemia was another disease of the same class. The description of the lesions in this case was almost identical with that of some cases of status lymphaticus, although he had never before seen such widespread hyperplasia in the latter condition. Dr. Ewing had published a case some years ago, in which the lymphoid tissues were extensively hyperplastic, much more so in the Peyer's patches than in this instance, but in which there was no involvement of the nodes about the pylorus. The present case seemed to him suggestive as possibly standing between status lymphaticus and general lymphosarcomatosis.

DR. CELLER said that no bacteriological work had been done on the case. Neither blood cultures nor animal inoculations were made. Microscopic examination of the lymph nodes might at first suggest the possibility of the case being one of Hodgkin's disease on account of the slight increase in connective tissue, and the presence of multinuclear giant cells. Here, however, all resemblance between the two conditions ceased, and, as Dr. Ewing himself had said, the case was evidently not one of Hodgkin's disease. Marked hyperplasia of the Peyer's patches



is not uncommon in status lymphaticus, although both the gross and microscopic appearances differ from those presented by the demonstrated specimens. Against the diagnosis of lymphosarcoma may be cited the uniformity presented by the lymphoid cells, which correspond exactly with those normally present in the lymph nodes and intestinal tract; and the absence of karyokinesis, of metastases, and of infiltration of the muscular coat of the intestine as well as of the capsules of the lymph nodes.

## A STUDY OF CASES OF HODGKIN'S DISEASE AND LYMPHOSARCOMA.

W. T. LONGCOPE, M. D.

In presenting this subject, Dr. Longcope said that he felt some embarrassment by reason of the fact that he had so little new to show; but it had occurred to him that it might be of interest to give the results of a study of a certain number of cases of progressive enlargement of the lymph glands observed at the Pennsylvania Hospital, and to compare the pathological changes in the lymph nodes from these cases with the alterations in a series of lymph gland tumors which were now being investigated. The material for these latter observations had been kindly sent to him from a number of different laboratories.

Altogether at the Pennsylvania Hospital, twenty-five cases had been studied, in which the disease was characterized by a progressive enlargement of the lymphatic glands, either generalized or of a single group. These twenty-five cases had been followed, unfortunately, most of them to the autopsy table. Out of the twenty-five, the lymph nodes from twenty-one presented characteristic pathological changes, both in the gross structure and in the histological structure. These changes, which were later shown more readily by means of lantern slides, were much the same as those recognized for a number of years, but to which

Reed first called attention in this country, and considered characteristic of Hodgkin's disease. The pathological picture in all of these twenty-one cases had corresponded quite accurately, though there had been minor differences.

Four cases were of an entirely different nature. These cases were characterized by a growth in the lymph glands of a cell of one type. In three cases this was a large cell, much larger than the small lymphocyte, and almost as large as the cell which forms the mass of the germinal centers of the lymph follicles. The cell sometimes infiltrated the gland, though it did not replace the actual lymphoid structure. One case had died; two were still living and under observation. The fourth case represented still another type of growth. In this case the cells were small and somewhat irregular, and entirely replaced the lymphoid structure, forming, by an infiltration of the surrounding fat lobules, tumors which looked in themselves much like lymph nodes. The cells forming the growth showed numerous karyokinetic figures. This patient died within a year.

Dr. Longcope said that in this study he had excluded all cases of definite tuberculosis, as well as cases of syphilitic enlargements of the lymph glands, and cases of certain rare tumors of the lymph glands.

In regard to the diagnosis during life between some of these conditions, Dr. Longcope said that as every one had recognized, it was often a very difficult matter to differentiate between Hodgkin's disease and tuberculosis, Hodgkin's disease and lymphatic leukemia occasionally, and Hodgkin's disease and sarcoma—those cases in which there was a growth of one particular type of cell in the lymph glands. From tuberculosis, in the very vast majority of cases, the differentiation was not a very difficult matter; but certain cases of acute tuberculosis of the lymph glands it had been found very hard to differentiate from Hodgkin's disease. This type of tuberculosis, in which minute tubercles are scattered throughout the gland tissue, may be present for some months; the glands may not be very large and may be quite movable; but they usually at some time give pain, an im-

portant point in the differentiation of the condition from Hodgkin's disease. Without a histological examination of the gland itself or without a tuberculin reaction it may be impossible to differentiate the two conditions. From another type of glandular tuberculosis it was also difficult to separate these cases; that is cases in which there was an extensive caseation of a large number of lymph glands in various situations in the body. These cases may be differentiated by a tuberculin reaction.

From lymphatic leukemia it is always possible to differentiate cases of Hodgkin's disease by means of the blood count. Only during the remissions in lymphatic leukemia may the two diseases be confused. In the cases of Hodgkin's disease examined, there has usually been a polymorphonuclear leucocytosis; occasionally the leucocytes were low, 6,000 to 10,000; usually they were about 30,000. In two cases there was a moderately marked eosinophilia. Much stress could not be laid upon this fact, however, though it was interesting in connection with the presence of great numbers of eosinophiles in the lymph node tumors in some cases.

From lymphosarcoma it had been almost impossible to differentiate Hodgkin's disease from clinical examinations alone. None of the cases were diagnosed before the glands were removed.

To compare with these twenty-five cases, Dr. Longcope was now studying tissue from another series. So far examinations had been made of tissue from forty-seven cases. Of these, nineteen corresponded exactly with the findings in the twenty-one cases of Hodgkin's disease; seventeen apparently belonged to the sarcoma group, showing the growth of one particular variety of cell; two were definitely mixed celled sarcoma; and two were cases of lymphatic leukemia. The histories had shown that these last two cases, although they had remained for months with a low leucocyte count with only 20 to 30 per cent. of lymphocytes, had at times had as many as 30,000 to 60,000 leucocytes with 90 per cent. lymphocytes.

Finally, in reviewing the literature, seventy-four cases had

been collected, principally from German sources, in which the descriptions were quite accurate, and corresponded exactly with the type of curious granuloma-like tissue which had been found to be characteristic of the cases of Hodgkin's disease studied.

Dr. Longcope further said that the main problem at issue was the etiology of these conditions. He had inoculated animals—guinea-pigs and rabbits—with material from twelve cases of Hodgkin's disease, without finding tuberculosis in any of them. Monkeys had also been inoculated with lymph nodes from two cases, and the results were rather interesting, but not conclusive. After subcutaneous inoculation there was general glandular enlargement, which made its appearance in about three weeks; no changes occurring before that time. The glands became so large that they could be readily seen in the cervical region and in the axilla. Some of these glands were removed and showed histologically only simple hyperplasia. There were none of the characteristic lesions of Hodgkin's disease. After about two months the glandular enlargement subsided entirely. He had tried again to produce glandular enlargement with the same tissues, but after keeping the tissues on ice for several weeks they produced no effect when inoculated into monkeys. The fact that glandular enlargement could be obtained might depend simply upon the injection of large amounts of foreign cellular material.

Fresh tissue had been stained in many ways, and nothing characteristic of any organism had been found. Sections were stained by the Levaditi method but no structure which could be identified as spiral organisms could be found. No clue could be given, therefore, as to the etiology of the disease. However, it seemed at present that it would be much better to limit the term Hodgkin's disease to the type of tumor described, which is sufficiently characteristic to enable one to differentiate it from other type of growths in the lymph glands. Until something definite was known as to the etiology it was, of course, impossible to make any rational classification. Until then it seemed best to differentiate these cases of Hodgkin's disease from various types of sarcoma of the lymph nodes.



*Discussion.*

DR. F. C. WOOD said that he had recently seen a case in Dr. John S. Thacher's service at the Roosevelt Hospital which was of interest in this connection. The autopsy was performed by Dr. Hodenpyl. The patient was a young boy on whom a diagnosis of anemia had been made. The only lesion found was enlargement of the spleen, which contained large yellowish masses and a few hard lymph nodes. None of these nodes were very large but they were very hard. The bone marrow was not involved. The microscopic sections of the spleen showed large Malpighian follicles with lymphocytic type of cells. The yellowish areas were dense connective tissue with some necrosis and some hyalin degeneration. The nodes were almost entirely fibrous tissue. In a few small areas in each node there were areas of lymphoid tissue with a few large cells with lobulated nuclei as in the ordinary Hodgkin's disease. There was no lesion in the intestine and except for the general anemia the lesions in the spleen and lymph nodes were the only ones found.

DR. JAMES EWING said that he would prefer not to attempt to discuss the subject without notes, and would rather simply express his gratification at having listened to the presentation. He might perhaps tell of his own experience with cases clinically called Hodgkin's disease. They were very common in New York. As Dr. Longcope had said, we are very much in doubt as to what cases to group together. Dr. Ewing's own rule was when such nodes were sent to the laboratory for examination to class as Hodgkin's any case with a clinical diagnosis of Hodgkin's unless it showed a perfectly definite lesion of some other type, as sarcoma. Of the group classed as Hodgkin's the majority were found to be of the giant cell type, though a large proportion were of the small cell type without giant cells, pure lymphocytes, with obliteration of the lymph follicles. Some showed very marked development of giant cells; others showed marked development of hypertrophied endothelial cells. He had recently seen such a case from the New York Hospital, in



which almost the whole tissue was made up of endothelial cells. In other cases the numbers of eosinophiles were astonishing. There were in this group of cases a number of other very peculiar histological structures, the significance of which he was quite unable to determine. In regard to the etiology, Dr. Ewing said that his own belief had been very much colored by a publication by Sternberg, in which was described a peculiar type of tuberculosis of the lymph nodes, exhibiting the histology of giant-cell Hodgkin's disease. The clinical history was similar to Hodgkin's disease, and tuberculous infection had been demonstrated. He did not share the belief of those who held that tuberculosis had been eliminated as an etiological factor in Hodgkin's disease. He had looked over many slides in the search for tubercle bacilli, but the results were almost invariably negative. In studying one case which had been sent to him, Dr. Ewing had spent an entire afternoon searching the sections, and had finally succeeded in getting a few acid fast bacilli in the nodules in the liver. His own feeling was that eventually it would be found that this disease falls into the group of peculiar lesions of tuberculosis. He had inoculated animals with the nodes repeatedly, and the results had not been entirely negative. Dr. Ewing thought Dr. Longcope's contribution most admirable, and hoped that he would continue his experimental study and throw still further light on the etiology.

DR. RICHARD M. PEARCE said that as most of his knowledge of Hodgkin's disease had been obtained from Dr. Longcope while he was associated with the latter in pathological work in Philadelphia, he had nothing of value to add to the discussion. In regard to Dr. Ewing's remarks as to the possibility of a tuberculous nature of the lesions, Dr. Pearce said that he had thought that this opinion had been rather generally set aside. He believed the differentiation which Dr. Longcope had attempted, even though it were not final, was of great value, because it gave two or three groups into which doubtful cases could be thrown until etiological or other investigations offered a sound classification of these puzzling affections of the lymph nodes.

DR. E. LIBMAN referred to a few cases of some interest which he had seen. One was a case of Hodgkin's disease with a high leucocyte count, 35,000 to 40,000, with high polynuclear percentage. The patient was intensely jaundiced. At autopsy destructive and secondary fibrous changes in the tissue were very marked, apparently due to long-continued X-ray treatment. The X-rays had been applied to the axilla and the enlarged glands had disappeared. The high polynuclear count was interesting, as there was no diffuse polynuclear infiltration in the tissues. Cases in which the lesions were confined to the abdomen were also of interest. In one interesting case which he had seen the patient had pain in the abdomen and was jaundiced, and was operated on for supposed gall-bladder disease. Large lymph nodes were seen, and the post-mortem showed Hodgkin's disease, although the lesions themselves showed no tubercle bacilli. The patient was a man who had had continued fever, and hemorrhages from the nose and throat. The patient stated that he had had lymph nodes removed from the right axilla two years before. The lymph nodes in the left axilla were enlarged and there was some bleeding from the nose and throat. The white cell count was about 5,000; the red cells were increased in number and the hemoglobin was over 100 per cent. The question arose as to how to account for the polycythemia, and the most likely thing seemed tuberculosis. It was thought that the symptoms were due to a miliary tuberculosis, and before the patient died miliary tubercles were found in the choroid. The post-mortem showed general miliary tuberculosis which was very extensive. There was a new formation of red blood cells in the bone marrow; and a most interesting thing was that the lymph nodes at the root of the mesentery contained old cheesy foci. In some of them the cheesy areas were surrounded by tissue quite typical of Hodgkin's disease. His own experience had been similar to that of others in that he had not been able to prove tuberculosis to be the etiological factor. He believed in grouping together all of these cases as Dr. Longcope had suggested. The problem was the same as in certain cases of icterus

and the erythema group. It was probable that although a number of cases in the group were due to one cause, other causes could produce similar lesions.

DR. LONGCOPE said that Dr. Ewing had spoken of caseation in some glands. They had seen this condition several times, and in two cases had inoculated guinea-pigs with masses of material and portions of the glands, but had not found tuberculosis. There was a type of necrosis which sometimes occurred in these cases, but so far he had not been able to show that this was due to the tubercle bacillus. Dr. Libman had mentioned the effect of the X-rays upon these glands. This he had noticed in one case. It was quite remarkable to see the change which took place in the glands. The lymphatic tissue apparently disappeared. A gland removed after X-ray treatment showed a curious fibrous condition with a few masses of cellular material scattered here and there. The lesions which had been strictly confined to the abdomen they had not seen very frequently. In only one case were the spleen and mesenteric lymph nodes found enlarged; this patient had come to autopsy. In another case there was involvement of the inguinal glands and of the retroperitoneal.

---

**Proceedings**  
of the  
**New York Pathological Society.**

---

New Series, Vol. VIII.      December, 1908; January, 1909      Nos. 7 and 8

---

TABLE OF CONTENTS

HOWLAND AND RICHARDS, An Experimental Study of the Metabolism and Pathology of Delayed Chloroform Poisoning.—MARTLAND, A Case of Congenital False Diaphragmatic Hernia.—RYTTENBERG, On the Value of the Use of Ammonium Oxalate in Blood Culture Technique.—CECIL, A Study of the Pathological Anatomy of the Pancreas in Ninety Cases of Diabetes Mellitus.

DR. E. LIBMAN, *President.*

---

AN EXPERIMENTAL STUDY OF THE METABOLISM  
AND PATHOLOGY OF DELAYED CHLORO-  
FORM POISONING.

JOHN HOWLAND, M.D., NEW YORK, AND A. N. RICHARDS, PH.D.,  
CHICAGO.

(*From the Laboratories of Pharmacology and Pathology of the College of  
Physicians and Surgeons, Columbia University, New York.*)

In the course of some investigations which have occupied the attention of Dr. A. N. Richards and myself during the past four years, we used prolonged and repeated inhalations of chloroform in an attempt to diminish the oxidative power of the cells and thus to inhibit or prevent the transformation of certain

substances with which we were experimenting. We found, however, that a number of control animals which received chloroform alone were profoundly affected and died after a lapse of hours or days after their return to consciousness and that they all exhibited severe parenchymatous lesions, especially in the liver. In other words, we produced typical delayed chloroform poisoning. It appeared to us advisable, in view of the great importance attaching to delayed poisoning, to study the metabolic changes occurring as a result of this, and in comparison with the pathological lesions produced. Dogs, upon which metabolic experiments are most easily carried out, can also be regularly so anesthetized as to cause their death many hours after the anesthesia.

The conception of delayed chloroform poisoning has been of slow development. Although Casper<sup>1</sup> and Langenbeck<sup>2</sup> in 1850, and Mouat<sup>3</sup> in 1856 spoke of a postponed fatal effect of chloroform, it was not until more than thirty years later that the condition began to be generally recognized and accepted. Thiem and Fischer<sup>4</sup> in 1890 also reported a fatal case due, they believed, to the delayed effect of chloroform. In the following year Bastianelli<sup>5</sup> reported three cases, and in 1892 Fränkel<sup>6</sup> reported several more. Thereafter reports appeared in rapid succession by Ambrosius<sup>7</sup>, Guthrie<sup>8</sup>, Bandler<sup>9</sup>, Marthen<sup>10</sup>, Heintz<sup>11</sup>, Steinthal<sup>12</sup>, etc. In England Guthrie's paper first called attention to the condition, and in this country cases have been reported by Brewer<sup>13</sup>, Bevan and Favill<sup>14</sup>, Holmes<sup>15</sup>, Cushing<sup>16</sup>, Ballin<sup>17</sup>, Wells<sup>18</sup> and others. It is undoubtedly true that some deaths have been reported as due to chloroform which could, with greater probability, be referred to some other cause, such as the original disease or the strong antiseptics employed; but this does not affect the validity of the majority of reported cases.

It is held, and the published accounts bear this out, that the liver changes in fatal human cases vary according to the age of the patient; that those in the very young differ from those in older children or adults in the *absence of necrosis*. It is dif-



difficult to understand such a selective action. Two explanations are possible: The first is that in young children the duration of symptoms is usually less than twenty-four hours; and it may be that death occurs before the lesions have had full time to develop. The second is that the majority of instances of this type were reported before the necrotic nature of the lesions was well recognized (1896) and the published autopsy findings were very incomplete and unsatisfactory.

It seems likely that in some instances at least the true character of the lesions was not recognized. Guthrie<sup>19</sup>, in his second paper, reported the case of a child, three years old, who died eighty-four hours after operation. Fatty changes in the liver are alone described, but a photomicrograph is given of a section stained for fat, in which the whole center of the lobule seems necrotic. Nevertheless it must be admitted that there are on record fatal cases of delayed chloroform poisoning which showed at autopsy, so far as reported, only fatty changes in the liver. In the older or so-called cholemic type the lesions in the parenchymatous organs, especially the liver, are severe and vary in the different cases only in degree. There is almost always an intense icteric discoloration of the skin. There may be cutaneous hemorrhages; and hemorrhagic extravasations into the serous membranes of the abdominal and thoracic cavities are frequently found. There may also be areas of hemorrhage in the gastrointestinal tract. The heart is seldom macroscopically altered. With appropriate staining, fat in greater or less quantity may be demonstrated in the fibers. The kidneys always suffer to a certain extent, though the evidence is frequently only microscopical. Whatever fatty change is present is apt to be in the collecting tubules. The cells of the convoluted tubules show all degrees of degeneration, and scattered cells may be necrotic. The glomeruli escape.

The volume of the liver varies with the duration of symptoms. The longer death has been postponed, the smaller is its size. The color is usually strikingly yellow, "safron" or "ochre colored" it is often called, and at times it is mottled with pink-

ish areas. On cross section the lobular markings may be difficult to distinguish, or it may be noticed that the lobules are yellowish or grayish at the periphery and reddish in the center.

Under the microscope all grades of destruction are found, from the slightest necrosis in the center of the lobule to almost complete dissolution of the whole parenchymatous structure of the organ. The essential lesion is necrosis; it begins at the center of the lobule and advances centrifugally. In some instances, those that have been described as acute yellow atrophy, the liver structure has been almost unrecognizable. At the periphery of the lobule in contact with the portal spaces are cells retaining their normal form and staining properties, but all the cells not necrotic are heavily loaded with fat. The protoplasm of the necrotic cells may be retained and stain deep pink with eosin, or it may have been almost entirely removed and only a narrow rim be left around the fragmented nucleus. The center of the lobules may show great congestion and even hemorrhage. In striking contrast to this destruction of parenchymatous cells is the normal condition of the bile ducts, blood vessels, and connective tissue.

Nothnagel<sup>20</sup>, in 1886, was the first to study the lesions produced by chloroform in animals. His experiments were badly planned in that he gave chloroform by mouth and subcutaneously, and not by inhalation. The amount that he employed was, moreover, so very large that most of the animals died in a few hours, or were killed at that time. Nevertheless he produced fatty changes in the heart, liver, and kidneys.

The first attempt to explain delayed poisoning was made in 1883 by Ungar with the help of Junkers<sup>21</sup>. He appreciated the great difficulties in the way of separating symptoms and pathological changes due to chloroform, from those due to the primary disease or injury necessitating operation, and therefore decided to use animals. His experiments were carefully planned and carried out, and his results were of great importance. He administered chloroform by inhalation to rabbits and dogs, and was able to produce great fatty changes in the

liver and heart and less in the kidneys. Unlike most subsequent investigators, he let his animals die, and so obtained more severe lesions than have those who after twenty-four, forty-eight, or more hours, killed their animals. Like many who followed him, it is evident that he began with a preconceived idea as to the organ most probably responsible for death, and wrote his descriptions of lesions from that standpoint. He found great change in the cardiac muscle and inclined to this as the cause of death. From his description of the appearance of the livers, both macropscopical and microscopical, it is apparent, however, that in them very severe lesions were present. He says that the center of the lobules was made up of only fatty detritus, the cell outline was indistinguishable.

In 1889 Ostertag<sup>22</sup> and Strassmann<sup>23</sup> independently confirmed Ungar's findings.

Thiem and Fischer<sup>24</sup> in 1890 used rabbits and dogs and produced marked fatty changes, especially in the livers. In 1896 Bandler<sup>25</sup> and Heintz<sup>26</sup>, independently, recognized necrosis in the livers of fatal human cases and produced necrotic lesions in the livers of dogs and rabbits. From this dates the recognition of necrosis as the most important of the changes produced by chloroform. In fact hardly an autopsy has been reported since that time that has not shown necrosis, and in many it has been so marked that the cases have been denominated acute yellow atrophy.

There has been practically complete agreement among all writers during the last ten years that the most extensive changes are produced in the liver, and that here is to be found the chief cause of death. Offergeld<sup>27</sup> alone dissents from this view and thinks the kidneys the organs chiefly involved.

There is no record in the literature, so far as we know, of a study of the metabolism in animals in which such a condition of delayed chloroform poisoning has been experimentally induced. The metabolic effects of chloroform given by mouth, by subcutaneous injection, or by inhalation, have been widely studied, but in every case normal, uneventful recovery apparently

occurred. Strassmann<sup>28</sup> made estimations of the urinary nitrogen before and after chloroform inhalation. There was a marked increase in the nitrogen excreted. Salkowski and Taniguti confirmed this. Kast and Mester<sup>29</sup> examined changes in the sulphur excretion after anesthesia with chloroform in human subjects. They found marked changes in the ratio of sulphate sulphur to neutral sulphur, the latter form being increased greatly in amount, the former being little affected.

In 1897 Vidal<sup>30</sup> published the results of a very comprehensive study of the effect of chloroform on metabolism. Some of the methods which he used are now open to serious criticism. Urea, for example, was estimated by the hypobromite method, and creatinin by the old Neubauer method. The results of a number of observations on human subjects showed total nitrogen to undergo a marked increase, usually greatest on the second day after the anesthesia. These results were confirmed in experiments on dogs and rabbits. His results on the distribution of nitrogen in the urine and the experiments which he made to determine the causes of variations in the different urinary constituents can not be regarded as convincing. His results on sulphur elimination confirmed those of Rudenko, Kast and Mester, and Savelieff.

Paton's<sup>31</sup> recently published series of experiments was directed specifically towards the elucidation of the question of delayed chloroform poisoning. Dogs in a condition of nitrogenous equilibrium were poisoned with chloroform by inhalation, by mouth, and by subcutaneous injection. When given by inhalation for one, two or three hours there was an increase in urinary nitrogen. Changes in ammonia nitrogen were not constant, creatinin excretion was parallel with total nitrogen, and sulphur was not changed. When twenty grams of chloroform were given by mouth on two consecutive days greater changes were produced. He considers that these experiments show a direct toxic action on the liver, and believes that the greater metabolic toxicity of chloroform given by mouth indicates that if chloroform given by the lungs is not eliminated with normal rapidity serious in-

juries might be effected which would lead to symptoms of late chloroform poisoning. He suggests that delayed eliminations occurred in his experiments in which chloroform was given by mouth, because of unusually firm fixation of chloroform by the proteids of the tissues. He expressed the belief that late chloroform poisoning may arise as the result of chloroform given by inhalation, if elimination of chloroform by the lungs is delayed owing to respiratory deficiency or to unusually firm fixation of chloroform by the tissues. His hypothesis is not convincing, because the records fail to show that respiratory deficiency is a constant feature in anesthesia, followed by delayed poisoning in man; no suggestion is offered as to the possible nature of an "unusually firm fixation" of chloroform by the tissue proteids, and the experiments of Moore and Roai<sup>32</sup> show that this fixation is dependent only upon the vapor pressure of chloroform.

Further chemical evidence regarding late chloroform poisoning is furnished by Taylor<sup>33</sup> and by Wells<sup>34</sup> who analyzed livers, obtained at autopsy, from cases in which death was due to this condition. Taylor was able to isolate leucin, tyrosin, and arginin in relatively large amounts. Wells separated histidin, leucin, tyrosin, glycocoll, and glutamic acid.

The experimental results cited lead to the conclusion that a marked increase of protein katabolism is caused by the action of chloroform upon the tissues, which is independent of the narcotic properties of the substance. The increased katabolism persists for a relatively long time after the administration of chloroform. When chloroform is given by mouth, its effect upon metabolism is more intense than when given by inhalation. It is logical to believe that this fact is due to the greater concentration in which chloroform reaches the liver when given by this path.

It is a striking fact that in none of the experiments upon which these conclusions are based had late poisoning actually been produced. In the papers in which attention has been directed towards this condition it is assumed that a mere intensification of the observed effects of chloroform will lead to the condition of late poisoning. Direct evidence concerning the na-



ture of the condition is necessary in testing the truth of this assumption. The observations that necrotic changes in the liver may constantly be found after chloroform anesthesia in dogs, and that dogs severely poisoned may die from the late effects of the anesthetic, led us to the hope that by producing the condition experimentally, by studying the morphological changes and the urinary excretions, and by comparing these results with those similarly obtained in animals in which recovery from severe poisoning was normal, we could discover in what respects the phenomena of late poisoning are to be differentiated from those of a normal anesthesia.

We have succeeded in making such a study in two dogs in which fatal late poisoning was developed, and in one dog in which severe poisoning, followed by normal recovery, occurred.

I shall give only a brief résumé of the experiments.

#### *Metabolism Experiments.*

*Methods:* The animals used were dogs. On account of the frequency with which vomiting occurs after anesthesia with chloroform, no food was given during any of the experiments. Osterberg and Wolf<sup>35</sup> and Underhill and Kleiner<sup>36</sup> have shown that the metabolism of fasting dogs is practically constant from a day or two after the beginning of starvation, for many days. Water was given *ad libitum*. Most of the urine was collected by catheter. In none of the experiments was there evidence of an infection of the bladder.

Chloroform (Squibbs', for anesthesia) was administered by an open cone, and enough was given to produce and maintain surgical anesthesia. The actual amounts of chloroform used and the percentage strengths of the chloroform inhaled were not estimated.

Total nitrogen was estimated by the Kjeldahl method; urea, ammonia, creatinin, and creatin by the methods of Folin. The different forms of sulphur were estimated as barium sulphate following the procedures recommended by Folin.

*Description of Experiments.*

**Experiment 1.**

WHITE BULL-BITCH PUP.

Normal period, June 11 and 12. Chloroform administered on June 13, for two hours in the morning and for an hour and a half in the afternoon. Total period of anesthesia, three hours and a half. Recovery from both anesthetics was normal. The following morning the animal appeared normal except for weakness and general depression. No vomiting occurred.

During the after period, June 14 to 16, no noteworthy symptoms occurred. There was no vomiting.

At the end of the experiment, the animal, apparently perfectly well, was killed with ether, and the autopsy performed immediately.

*Autopsy:* Animal much emaciated. Heart and lungs, stomach and intestines, pancreas and spleen, appeared normal. Liver apparently of normal size; surface smooth; consistency about normal; color strikingly yellow; cut sections showed lobulations plainly; centers of lobules appeared grayish and periphery very yellow. No congestion. Kidneys were of normal size and consistency; surface normal.

*Microscopical Examination. Liver:* This is very fatty. The fat is chiefly, but not entirely, confined to the periphery of the lobules. Stained with hematoxylin and eosin, it is seen that around the interlobular space in the periphery of the lobule the liver cells retain well their form and staining properties. In the intermediary and central zones great changes have taken place. The liver cells are in all stages of degeneration. Some show only a faintly staining nucleus and the reticular structure of the cell; in others both the nucleus and the protoplasm stain very badly. Other cells consist only of a shrunken and distorted and deeply staining nucleus surrounded by a very narrow rim of protoplasm. From some intercapillary areas the cells have entirely disappeared. Confined almost entirely to the intermediary and central zones of the lobules are scattered giant cells containing within themselves masses which stain dark blue with hematoxylin. These masses are soluble in dilute acetic acid without the production of gas bubbles, stain black with a dilute solution of nitrate of silver, and are therefore composed of calcium phosphate. Only in a few instances are they found among the apparently healthy cells. The number of these in each lobule varies between ten and fifty. The capillaries in the central zones contain a few red blood cells. There are no thromboses.

*Kidneys:* There is a moderate fatty deposit (not much more than is ordinarily found in dogs) in the cells of the limbs of Henle's loop and in the collecting tubules. The glomeruli are normal. There is a marked degenerative change in the cells of the tubules, especially of the convoluted tubules. Many tubules contain fragments of cells and casts.

*Heart:* The muscle retains its transverse striations.

*Gastrointestinal tract:* Normal.

## Experiment 2.

### FULL GROWN FOX TERRIER BITCH.

Normal period, June 23 and 24. Chloroform administered on June 25. The administration of chloroform was begun at 9:38 a. m., and continued until 12:08 p. m. Chloroform was again given from 4:10 to 6:10 p. m. Total duration of anesthesia, four and one-half hours. Recovery from the effects of the anesthetics was slow but uneventful.

After period, June 26 to 28. Vomiting occurred after water was taken on June 26. No vomiting occurred on June 27 and June 28. Feces containing old blood were passed on June 27.

Second chloroform day, June 29. Chloroform was administered for one and a half hours in the morning, and again for one and a half hours in the afternoon. Total duration of anesthesia, three hours. Recovery was slow. On the following morning, at 7:30 a. m., the animal could stand and walk about, and except for weakness and general depression appeared to be normal in her behavior. From 8:30 a. m., until death occurred at about 10 a. m., she was completely prostrated, and during this time frequent convulsions occurred. They began with increase in depth and frequency of respiration, twitching, and rigidity of the neck muscles; then followed clonic spasms of the legs, and finally a tetanic condition of the whole body. In the intervals between the convulsions prostration was very great, and the animal was unconscious; but the reflexes were retained. During this time black fluid feces consisting of old blood were passed. Vomitus of a similar character was ejected. Death occurred at 10 a. m.

*Autopsy:* Made immediately after death. The animal was not greatly emaciated, subcutaneous fat being fairly abundant. Heart and lungs appeared normal. The peritoneum was smooth and glistening. The omentum was congested and in it two small areas of hemorrhage were found. It was dotted here and there with typical fat necroses in all stages of formation; none exceeded 4 mm. in diameter. These necroses were found in the fat surrounding the pancreas, within the pancreas itself, and in the mesentery of the colon. The pancreas was very firm and pale. There was no sign of obstruction in its ducts. The gall bladder was full of greenish bile. The cystic and common ducts were patent. The liver was of normal size and very yellow. On the surface and on a cut section it was dotted with very numerous reddish areas of pin-head size, which were evidently in the center of the lobules. The spleen was normal. The cortex of the kidneys was slightly yellowish in the neighborhood of the pyramids; otherwise the kidneys appeared normal. The stomach contained hemorrhagic material, but the mucosa appeared normal. The whole intestinal tract was full of hemorrhagic material. The mucosa of the entire small intestine was hemorrhagic.

*Microscopical Examination. Liver:* There is not a normal parenchymatous cell to be found in any of the sections. About the portal spaces are a few small islands of cells that retain their approximate form and staining properties, but are very fatty. There are hemorrhagic areas oc-

cupping the center of the lobules. Within these areas the liver cells are in all stages of dissolution. Many are swollen, their nuclei disintegrated or absent, and stain deep pink with eosin. Others have degenerated to amorphous masses. The remainder of the lobules are composed of swollen cells, of which only the nuclei and the reticular structure of the cell may be seen. Scattered among these hydropic cells are others that stain deep pink and are without nuclei. In the hemorrhagic areas only a few small masses stain red with Scharlach R, while in the periphery most of the cells stain deep red. No thromboses are found.

*Kidneys:* These contain rather more fat than in Dog 1, but in the same situation. The same changes are to be found in the tubules as in Dog 1.

*Pancreas:* The substance of the pancreas itself is normal. In the fat immediately surrounding the pancreas and in the omentum and mesentery are small hemorrhages and typical fat necroses.

*Heart:* Muscular striations are present in the heart muscle.

*Gastrointestinal tract:* The mucous membrane is congested throughout. In the stomach and large intestine a few hemorrhages are seen; in the small intestine they are almost continuous throughout its whole extent.

### Experiment 3.

#### YOUNG WHITE BULL-DOG.

Normal period, July 4 and 5. Chloroform day, July 6. Chloroform given for three hours in the morning and two and one-half hours in the afternoon. Total duration of anesthesia, five hours and a half.

After period, July 7 and 8. During July 7, vomiting occurred very frequently after water was taken. The vomitus did not contain blood. Feces passed on July 7 contained both fresh and old blood. Aside from weakness and these gastrointestinal symptoms, the animal appeared normal. On July 8, until 4:00 p. m., the animal was conscious and apparently normal except for muscular weakness and gastrointestinal symptoms. She stood or walked with difficulty. Vomiting was frequent; the vomitus contained bloody mucus. At about 4 p. m. she became nearly unconscious. She lay on her side and at intervals whined in a semi-conscious manner, snarling and biting aimlessly at the floor of the cage. The respiration was very rapid, sometimes deep and labored. In the evening, at about 9:30, she was unconscious. Her stupor was interrupted by periods of delirious crying, aimless and unconscious or semi-conscious attempts at biting, and incoordinated muscular movements. Death occurred during the night, and on the following morning she was found in a state of rigor.

*Autopsy:* Made soon after the death of the animal was discovered. Emaciation was not extreme. Hemorrhagic extravasations were found in the tissues of the mediastinum and pleura. The lungs were normal. The pericardium and epicardium contained hemorrhagic areas. The myocardium was pale. The omentum showed areas of marked congestion and contained a few scattered points of hemorrhage. There were numerous areas of hemorrhage in the mesentery. The liver was apparently somewhat

smaller than normal. Its substance was soft and easily friable. In appearance it resembled that of Dog 2, being very yellow with reddish areas at the center of the lobules. The kidneys were of normal size, the tissues somewhat soft, and the cortex pale in color. The stomach contained bloody material of fluid consistency; its mucosa was slightly congested. The intestines were filled with blackish fluid material, evidently consisting chiefly of blood. An accurate judgment concerning the condition of the intestinal mucosa was difficult on account of post-mortem change, which was considerable.

*Microscopical Examination. Liver:* This is greatly altered. At the periphery of the lobules the cells stain well, but are very fatty. The inner two-thirds of each lobule are hemorrhagic. In the hemorrhagic area the cells are swollen, stain deeply with eosin, and are without nuclei. Giant cells containing calcium phosphate are present in the hemorrhagic areas, but are confined to their periphery and are not found in the center. No thromboses are to be seen.

*Kidneys:* These are greatly congested. There are small hemorrhages in the cortex as well as the pyramids, and one or two within the glomeruli themselves. In other respects, the changes are like those that have been described.

A faint reaction for albumin was obtained in the urine of each dog on the days on which chloroform was given. The urine showed a slight reducing power when tested with Fehling's solution on these days. The urine of each dog on the days on which chloroform was administered was highly colored and gave strong reactions for bile pigment. This reaction persisted until the end of the experiment, and in the cases of Dogs 2 and 3 was very intense. Gerhardt's test for diacetic acid and Legal's test for acetone were negative in every urine. Every urine was acid to litmus.

The limits of this paper do not include a consideration of the symptoms exhibited by human cases, but a word in regard to the similarity with them of those observed in our dogs may be allowed.

In the so-called cholemic or adult type of the delayed poisoning, a longer or shorter uneventful period is the rule; and so it was with both of our dogs. With Dog 3 at least forty hours intervened after the anesthetic before untoward symptoms appeared, and during this time it was impossible to detect any difference from the recovery from any severe narcosis.



Human cases become wildly delirious and occasionally have convulsions, and coma ends the scene. The signs of mental disorder or the equivalent of mental disorder in a dog were seen in both of our cases. In Dog 2 there were convulsions, and in Dog 3 purposeless attempts to bite and snarling and howling. Coma supervened in both instances. The vomiting of blood and the bloody stools, and the large amount of bile pigment in the urine are common to both animals and human beings.

### *Summary of Results.*

For the sake of brevity I will summarize the metabolic results of the three dogs. I would like to emphasize again that the first one had recovered so far as the metabolism and symptoms were concerned, and therefore makes an admirable control, while the other two dogs died of delayed poisoning.

First, as to *nitrogen excretion*. All experiments are alike in that they give an increase in katabolized nitrogen on the day of poisoning. On the day *after*, in every experiment, a still greater increase occurred (54 per cent. in Experiment 1; 76 per cent. in Experiment 2; and 185 per cent. in Experiment 3). On the third and fourth days in Experiment 1, a gradual decrease to normal took place. In Experiments 2 and 3, the nitrogen estimation remained high until the end. But the mere total loss of nitrogen alone can not be the cause of death, for an animal can stand very easily the loss of nitrogen shown in these experiments, under simple starvation.

*Urea and ammonia*. It is surprising to see how closely the excretion of urea nitrogen follows total nitrogen. It is true that on the day after poisoning in each case, there was a diminution in the relative excretion of urea nitrogen; but it was only slight and tended to return again to the former percentage figure. The percentage excretion of urea was always within normal limits. On the day following the poisoning there was a divergence of the urea curve from that of total nitrogen, the percentage decrease was not always compensated for by a percentage increase in the ammonia. There was an actual increase in ammonia nitrogen on

each day on which chloroform was given, but it was not proportional to the increase in total nitrogen, and hence in every case a percentage decrease was found. A greater increase in ammonia nitrogen occurred in every experiment on the day following chloroform, so that in Experiment 2 the percentage returned to normal; and in Experiments 1 and 3 it slightly exceeded normal. In Experiment 3 the percentage again sank, while in Experiment 1, the dog which recovered, it remained high. It is very surprising to see so little change in ammonia; in Experiment 3, the pure delayed poisoning, it was within normal limits throughout.

In human cases there can be no doubt that ammonia nitrogen would be very much increased on account of the diacetic and oxybutyric acids present, but these were entirely absent in our dogs.

The undetermined nitrogen, representing the purins, uric acid and amino acids, increased in each experiment on the day of anesthesia. The percentage on this day was high in all and much above normal in Experiment 2. A still greater absolute increase took place on the day following chloroform, which was enough in Dogs 1 and 2 to make a percentage increase, but not in Dog 3, in which a decrease in percentage value occurred. The fact that there was no greater increase in undetermined nitrogen in the fatally poisoned Dog 3 than in the control tends to lessen the emphasis that might otherwise be laid upon this increase.

Our figures show that if the increased nitrogenous excretion is due to autolysis, this may occur to an abnormal degree without causing great abnormalities in the distribution of nitrogen as urea, ammonia, and amino acids. Leucin and tyrosin were never found in the urine of these cases, but these have been missed in many cases of phosphorus poisoning, and there is no *a priori* reasoning why after chloroform poisoning the enzymes that split off ammonia from amino acids and convert it into urea should not still be active.

*Creatin and creatinin.* In Experiments 1 and 2 the absolute values for creatinin were almost constant throughout, an-

other instance in which this excretion may be unchanged even when large amounts of tissue protein are being decomposed. In Experiment 3 creatinin was constant on the two normal days and the chloroform day. It disappeared altogether on the day following anesthesia, but reappeared in small amount on the final day. These changes produced a marked decrease in the percentage values. The creatin was increased in every experiment on the day of chloroforming, and still more so on the following day. In Experiment 1 it returned to normal, but remained high in the other two experiments and continued to rise in Experiment 3, so as to be on the day of death more than three times the amount it was in health. With the present uncertainty as to the origin and indications of creatinin and creatin, it would be hazardous to draw conclusions. The greatly increased creatin undoubtedly has its source, as Benedict, Shaffer, and Mellanby believe, in the creatin of the muscles when rapid loss of muscle protein is going on, which is certainly the case after chloroform. The possibility must be borne in mind that the chloroform may have interfered with the formation of creatinin, and our figures may be considered as supporting in a measure the view of Mellanby that the liver is the organ chiefly concerned in the formation of creatinin.

*Total sulphur.* On the day of chloroform poisoning in each experiment, the increase in neutral sulphur was greater than the increase in sulphate sulphur. On the day following chloroform in Experiment 1, recovery of the normal sulphur relations began. In Experiment 2, a decrease in sulphate sulphur occurred while neutral sulphur underwent a still further increase. In Experiment 3, on this day, both increased. The second day of chloroform in Dog 2 was marked by changes in the sulphur excretion similar to those on the first chloroform day. It is obvious that we have not only a great increase in the amount of total sulphur, but a disturbance in the percentage distribution. It is interesting to compare the excretion of total sulphur to total nitrogen during the normal and poison days.

In Experiment 1, on the day of poisoning and the three

succeeding days, nitrogen equivalent to five and one-half normal days was excreted, but sulphur equivalent to six and one-third days.

In Experiment 2, in five days the equivalent of eight and one-sixth days nitrogen was excreted, but sulphur equivalent to eleven days.

In Experiment 3, in three days, seven and one-half days nitrogen was excreted and more than eight days sulphur.

All of this points to the fact that protein richer in sulphur is being katabolized in fasting. This has been found with other severe poisons. While it is constant immediately after chloroform in each instance, and was repeated in Experiment 2, the effect was no more prolonged or intense in the fatally poisoned Dog 3 than in the control.

We conclude from Experiment 1, the dog which recovered, that anesthesia with chloroform produces a very great increase in total nitrogen elimination, but that with the exception of creatin and creatinin the so-called partition of nitrogen-containing substances is normal. The sulphur excretion is also greatly increased and is carried out in an abnormal ratio. We see further from an analysis of the figures of Dogs 2 and 3, which died of delayed poisoning, that they differ from Dog 1 only in the degree and duration of the nitrogen excretion. They, too, with the exception of creatin and creatinin partitioned their nitrogen-containing substances in a normal manner, and Dog 1 exhibited the same abnormalities in the excretion of sulphur as Dog 3.

We are led to believe, therefore, that the metabolic differences between ordinary prolonged anesthesia and delayed poisoning are of degree only, and not of kind. We find further no basis for the widely disseminated view that cases of delayed poisoning are due to acid intoxication.

### *Pathological Results.*

From our experiments and those of others, it is plain that a single anesthesia with chloroform, of a duration of more than half an hour, induces fatty changes. These are demonstrable in



the liver in from twelve to twenty-four hours, reach their maximum in about forty-eight hours, and then gradually retrograde; but the excess of fat may be demonstrated for about two weeks. The fat appears first in central and intermediary zones of the lobule, and eventually may spread to the periphery and the whole lobule be intensely fatty. With more prolonged, and especially with repeated anesthetics, which are very much more destructive than single ones, necrosis appears. But, as is shown by two of our experiments, anesthesia of only one or two hours is sufficient, at least at times, to cause necrosis. The necrosis also begins in the center and extends centrifugally, so that almost all the cells may be necrotic and only a few around the portal spaces be still living.

The amount of protoplasm in the necrotic cells varies according to the length of time intervening before death. When this occurs promptly the cells may remain of almost normal size and contour. When longer delayed, the protoplasm diminishes markedly until there may be only the narrowest margin around degenerated nuclei which lie in the intercapillary spaces. The amount of hemorrhagic extravasation varies from none at all to a very considerable amount.

Very striking in two of our metabolism dogs were the calcium deposits and the giant cells surrounding them. These deposits were always in the necrotic areas and chiefly in the periphery of these. Their presence in less than forty-eight hours after poisoning indicates the rapidity of calcium deposition and engulfing cell formation. There is no mention of such deposits in pathological or experimental literature relating to chloroform. That they follow as a result of the chloroform is shown by the fact that we produced them in two instances.

In our second metabolism experiment mention was made of fat necrosis of the omentum and mesentery. There is no similar record in the literature. That fat necrosis sometimes occurs with hepatic poisons is shown by the reported observation of Wells<sup>37</sup> in regard to hydrazine poisoning. He produced in one dog small and scattered but typical fat necroses. Our result with chloroform stands as an isolated observation.



The changes produced in the kidneys and heart have been found, by other investigators and by ourselves, to be much less constant and severe than in the liver. From our experience it seems that there is not enough damage usually done to these organs to explain an interference with this functional activity.

We have found congestion and small areas of hemorrhage in the gastrointestinal tract frequently, and in one dog the whole small intestine was hemorrhagic. In this same dog were hemorrhages into the peritoneum, pleurae, pericardium, and mediastinal tissue. We have also found hemorrhages in the serous membranes of other dogs. The lesions found elsewhere are negligible.

It may thus be seen that there is a very great similarity between the human and the experimental lesions. In both they are most severe in the liver and consist of central necrosis and fatty degeneration, and, allowing for a certain difference in structure of the organ, are strictly comparable. The same may be said of the kidney lesions. In both of these there is also a tendency to hemorrhage into the serous membranes and into the gastrointestinal tract.

We have previously said that, from our metabolism studies, we were led to believe that the differences between the changes produced by prolonged anesthesia, and those produced by delayed poisoning, were of degree and not of kind. This view is strongly substantiated by the pathological examination. Dog 1, which was recovering and which served as a control, had changes exactly similar to those in Dog 3, but they were not so severe. That in this Dog 1, with the extensive liver lesions, the metabolism should have been normal at the close is remarkable and serves to show that metabolism may not be disturbed even by severe organic lesions in the liver.

Furthermore, the many experiments which we have made show unmistakably that any prolonged anesthesia with chloroform produces in the dog great alterations and even destruction in liver tissue, although there may be apparent perfect health. We believe that this is true of human beings as well as of animals.

## REFERENCES.

- <sup>3</sup>CASPER: *Woch. f. d. ges. Heilkunde*, 1850, xvi, 1, 17, 33, 49, 273.
- <sup>2</sup>LANGENBECK: *Behrend's Chlorof. Statistik*, Hanover, 1850.
- <sup>4</sup>MOUAT: *Med. Times and Gazette*, 1856, ii, 225.
- <sup>5</sup>THIEM AND FISCHER: *Deut. med. Zeitung*, 1889, x, 1111.
- <sup>6</sup>BASTIANELLI: *Bull. d. osped. di Roma*, 1891, x, 179.
- <sup>6</sup>FRÄNKEL: *Virchows Archiv*, 1892, cxxix, 254.
- <sup>7</sup>AMBROSIOUS: *Virchows Archiv*, 1894, cxxxviii, Suppl. Heft.
- <sup>8</sup>GUTHRIE: *Lancet*, 1894, i, 193, 257.
- <sup>9</sup>BANDLER: *Mitteil. a. d. Grenzgebieten d. med. u. Chirurg.*, 1896, i, 303.
- <sup>10</sup>MARTHEN: *Berl. klin. Woch.*, 1896, 204.
- <sup>11</sup>HEINTZ: *Inaug. Diss.*, Rotterdam, 1896.
- <sup>12</sup>STEINTHAL: *Jahrbuch f. Chir.*, 1896.
- <sup>13</sup>BREWER: *Annals of Surgery*, 1902, xxxvi, 481.
- <sup>14</sup>BEVAN AND FAVILL: *Jour. Amer. Med. Assn.*, 1905, xlv, 691.
- <sup>15</sup>HOLMES: *Appendicitis*, p. 215.
- <sup>16</sup>CUSHING: *Jour. Amer. Med. Assn.*, 1906, xlvii, 1191.
- <sup>17</sup>BALLIN: *Annals of Surgery*, 1903.
- <sup>18</sup>WELLS: *Jour. Amer. Med. Assn.*, 1906, xlvii, 341.
- <sup>19</sup>GUTHRIE: *Lancet*, 1903, ii, 10.
- <sup>20</sup>NOTHNAGEL: *loc. cit.*
- <sup>21</sup>UNGAR: *Vierteljahr. f. ger. Med.*, 1887, xlvii, 98. JUNKERS: *Inaug. Diss.*, Bonn, 1883.
- <sup>22</sup>OSTERTAG: *Virchows Archiv*, 1889, cxviii, 250.
- <sup>23</sup>STRASSMANN: *Virchows Archiv*, 1889, cxv, 1.
- <sup>24</sup>THIEM AND FISCHER: *loc. cit.*
- <sup>25</sup>BANDLER: *loc. cit.*
- <sup>26</sup>HEINTZ: *loc. cit.*
- <sup>27</sup>OFFERGELD: *Arch. f. klin. Chirurgie*, 1905, lxxv, 758.
- <sup>28</sup>STRASSMANN: *loc. cit.*
- <sup>29</sup>KAST AND MESTER: *Zeit. f. klin. Med.*, 1891, xviii, 469.
- <sup>30</sup>VIDAL: *Thèse de Paris*, 1897.
- <sup>31</sup>PATON: *Proc. of the Royal Soc. of Edinburgh*, 1908, xxviii, 472.
- <sup>32</sup>MOORE AND ROAF: *Proc. of the Royal Soc. of Edinburgh*, 1904, lxxiii, 383, and 1905, lxxvii, 86.
- <sup>33</sup>TAYLOR: *Univ. of Calif. Publ. Pathology*, 1904, i, 43.
- <sup>34</sup>WELLS: *Jour. Biol. Chemistry*, 1908, v, 129.
- <sup>35</sup>OSTERBERG AND WOLF: *Biochem. Zeit.*, 1907, v, 304.
- <sup>36</sup>UNDERHILL AND KLEINER: *Jour. Biol. Chemistry*, 1908, iv, 165.
- <sup>37</sup>WELLS: *Jour. Exper. Med.*, 1907, ix, 627.

*Discussion.*

DR. GEORGE E. BREWER, in discussing the clinical aspects of delayed chloroform poisoning, said that he considered these important for two reasons: First, because the disease itself is such a frightful one and the death-rate is so high; and, second, because its symptomatology is not generally understood, the cases being so exceedingly rare. As regarded the symptomatology, after a review of the literature, the cases could be classified under three general heads. 1. The type of disease generally seen in children and described by a certain number of authors, in which symptoms come on almost immediately and are associated with a profound degree of shock, the chief symptoms being prolonged vomiting, great prostration, coma, and death. In a certain number of cases acetone is found, but this is rare. High temperature may also be a symptom. 2. Another class of cases seen in children shows distinctly evidences of delayed poisoning. This class could best be illustrated by the history of one of Dr. Brewer's patients, a child about twelve years of age, with acute appendicitis, operated upon at the Roosevelt Hospital. The appendix was gangrenous and was surrounded by pus. There was limited peritonitis. The operation was short; chloroform was used; the patient was on the table for twenty minutes. He recovered from the anesthetic quickly. During the night he was comparatively restless; but there was then a drop in temperature, and he had a comparatively favorable day. The bowels moved; there was little vomiting. On the third day he seemed to be entirely convalescent. Urine was secreted freely. The mind was clear; and the child was hungry. He went to sleep in the early evening, and at twelve o'clock woke suddenly with a piercing scream. He looked about in a dazed condition, did not recognize anyone, and suddenly dropped into sleep again. In the morning he awoke again in the same way with a terrific shriek, evidently of abject terror and fright. He failed to recognize anyone and dropped into sleep again. This was repeated all day about every fifteen minutes or half hour. At night it was perfectly evident that the

child was in a very serious condition. There was a very decided odor of acetone in the breath, and the urine showed acetone and diacetic acid. During the following night the sleep deepened into profound coma, and the child died the following morning. In this case there was no vomiting and no fever. The chief symptoms were extreme restlessness, delirium of the wildest sort, gradually deepening coma, and a rise of temperature before death. On further investigation the child was found to be simply loaded with acetone and diacetic acid. This was the second type of cases, and represented the most frightful clinical picture which he had ever seen. 3. A third type of cases, Dr. Brewer had seen well illustrated in a patient, a man of fifty-six years, who had a moderate appendicitis. The operation was comparatively easy and short; and the patient took chloroform because of some damage to the kidneys. He did perfectly well for forty-eight hours; all symptoms disappeared; and he was considered thoroughly convalescent, when he suddenly became somnolent. When he woke up he seemed somewhat dazed. On the third day icterus appeared, and on the fourth day he was the color of an orange. The sleepiness increased to coma, and he died. An autopsy was fortunately obtained. The liver was rather small and very yellow. Almost no normal liver cells remained.

In reviewing the clinical histories of these cases, about ten or a dozen symptoms could be described, some of which appeared in all cases, some in only a few. Vomiting was quite generally present. Restlessness was almost invariably present in the beginning. The delirium was of the wildest sort, denoting great terror, and had been described as the delirium of delirium tremens by some authors. Icterus was sometimes present and sometimes absent. Coma was always the end, progressively deepening. Fever was not usually present, although in a few cases it had been exceedingly high, as high as 170° directly after operation. Cyanosis, air hunger, and dyspnea had been present in a certain number of cases, but were not symptoms to be relied upon. In the first class, where there were evidences of shock, it might be that there were other elements also present. But when

we consider late chloroform poisoning we must look for vomiting, restlessness, wild delirium, and coma. Acetone might or might not be present: when it was, it was usually associated with severe delirium. Since seeing his first case, Dr. Brewer had seen a few milder cases in which the patients were somnolent, with acetone in the urine, which then cleared up. He could recall three such cases. The severer cases almost invariably ended in death.

DR. JAMES EWING said that he had been told that when chloroform was first introduced Magendie declined to use it because he did not know what might happen after recovery from the anesthesia. Of course, such a precaution was ignored, and he had few or no followers; but the subsequent history has justified his scientific caution. Dr. Ewing thought that it was remarkable that, in spite of the fact that clinicians have been warned of the dangerous delayed action of chloroform, they have paid little attention to this condition. In England, especially, where one commission for the study of chloroform had been succeeded by another, and where Guthrie was repeating his warnings, there least of all was attention paid to this form of delayed chloroform poisoning. In France, in 1905, so-called cases of toxic appendicitis were described. The authors gave pictures of the lesions in the liver which were identical with the pictures shown by Dr. Howland. The clinical history of the three cases which they reported was identical with that described by Drs. Howland and Brewer, though the authors make no mention of such an explanation. These authors referred to Dieulafoy for corroboration of their views, but the evidence which they gave showed only that they were dealing with delayed chloroform poisoning. They quoted from half a dozen surgeons of France, each of whom had reported similar cases. In one case the diagnosis of hystero-epilepsy was made. The worst offenders in this field were the obstetricians, and though the warning had been sounded again and again, it had had very little effect upon the free use of chloroform. Dr. Ewing thought a considerable proportion of cases of toxemia of pregnancy were cases of delayed chloroform poisoning. He differed from Dr. Brewer



in regard to the frequency of the disease. He had no difficulty in finding material showing the lesions. He thought the condition was relatively common. The cases were seen at autopsy probably in larger numbers than were recognized in the wards. He had been much interested in the pathological anatomy shown in the sections. He thought possibly some information might be gained by a study of the nervous system in these cases. No doubt there were some observations of this sort, but he was not familiar with them. The important question was to what extent these observations made on dogs were applicable to man. It seemed certain that the dog was more susceptible to these lesions than was the rabbit. He had not been able to produce in the rabbit any such necrotic lesions as Dr. Howland had produced in the dog. Whether man is as susceptible as the dog or not, is not known. So far as the clinical course was concerned, the symptoms in dogs were reproduced in man as perfectly as one could demand. When the organs were examined the evidence was indisputable that exactly the same thing happened in man as happened in the lower animal. It was, therefore, justifiable to conclude that the toxic effects observed in the dog occur regularly and in the same way in man, though he thought caution should be used in attributing all such lesions to chloroform poisoning. These lesions could arise spontaneously without chloroform. If man were normally less susceptible than the dog, there was no question that the conditions which arise in man during which an anesthesia is used, render him much more susceptible. So that it is perfectly clear that the bearing of the previous condition of the patient on the choice of an anesthetic is most important. He had himself been most interested in the results of the metabolic studies, and had been surprised to find that there was so little change in the nitrogen, when according to the autopsy the liver was almost completely destroyed. He had this general objection to comparing the results of metabolism studies in dogs with the conditions which are met with clinically: One takes a dog in normal condition, and by administering chloroform rapidly produces severe lesions in the liver; and then one makes examinations of the urine and discovers that in

urine collected during the time in which the animal lives there is no change in the nitrogen; and he concludes that such changes can arise spontaneously without producing any change in nitrogen partition. This conclusion was, he thought, quite unwarranted. The metabolism in spontaneous diseases in which these marked lesions were found could not be deduced from observations of previously normal animals in which such lesions were rapidly produced by experimental methods of this sort. It was quite possible that in some of these cases the extreme destruction of the liver substance occurred only during the last few hours of life. Yet cases of acute yellow atrophy had been observed in which there was almost nothing left of the liver, in which the nitrogen showed very little alteration. The most important question connected with this work, it seemed to him, was the present status of chloroform. What is the case against chloroform? It seemed to be perfectly clear, and yet although it had been clear for years it needed iteration and reiteration, and such striking evidences as Dr. Howland had given, and especially such careful metabolism work as he and Dr. Richards had done.

DR. C. G. L. WOLF: Through the kindness of Dr. Howland, I have had the privilege of going over the results in the metabolism in delayed chloroform poisoning which he has presented; and while it may appear at first sight that the analytical results do not present changes commensurate with a fatal outcome, it seems to me that they are particularly instructive, in view of the direction which urine analysis has tended to take in the last few years. Instead of the routine analysis for urea by the hypobromite method, an accurate knowledge of the distribution of nitrogen is now desired, and this is given in the form of results similar to those of Dr. Howland. To what extent do Dr. Howland's results support this type of analysis? Dr. Howland finds in delayed chloroform poisoning: 1. That the liver, the principal gland involved in processes leading to metabolic changes which are represented in the urine by the formation of urea, is altered to such a degree that, microscopically, practically no cells with a capacity for functioning can be detected; 2.

That the results of the analyses by the methods to which I gave the name "nitrogen and sulphur partition" show a practically normal urine, although there is an obvious toxic destruction as shown by the nitrogen elimination.

If this be the case, we are confronted with a very serious question regarding the utility of this type of analysis for the purpose of diagnosis.

In the course of work to which my entire attention has been directed during the past four or five years, I have come across many conditions which bear out Dr. Howland's results in every detail. The first was brombenzol poisoning, a condition in many respects similar to cystinuria. In this toxic condition the liver is most profoundly changed, and yet the urine, with the exception of certain features, is not at all changed commensurately with the degree of liver destruction. The results were so anomalous that I decided, before publishing my conclusions, to take up normal metabolism as affected by different diets solely, and this investigation, part of which has been published, part of which is completed, but still unpublished, has taken over two years, and the work is by no means finished. I mention these details merely to show that it is absolutely necessary, before nitrogen partition can be used for diagnostic purposes, that the whole field of normal metabolism, as affected by diet and by the state of nutrition of the individual, be carefully investigated. This, so far, has not been done.

During the course of the work on normal metabolism I have investigated a number of other conditions which bear on this problem of the relation which the microscopical changes in the liver bear to the urinary findings. I have modified Lieblein's original experiment, in that I have temporarily clamped the common and cystic ducts, and have injected strong solutions of argyrol under pressure into the hepatic ducts. No change whatever was found in the distribution of nitrogen in the urine. Similarly I have performed a number of experiments with poisoning with carbon monoxid and with hydrocyanic acid, a poison which is believed to affect profoundly all katabolic activities,

without observing any change in the nitrogen partition. Lastly, in chloral hydrate intoxication leading to the death of the animal, the results, in so far as a general consideration of the nitrogen and sulphur analyses go, show that the poison is also without effect.

On the other hand, I have been able to produce very remarkable changes in the nitrogen and sulphur partition merely by the administration of suitable diets. These changes are greater than any I have found in the toxic states above mentioned, or in those which Dr. Howland has presented. It is pertinent, therefore, to ask what bearing these facts have on the general problem of urine analysis as applied to the diagnosis of changes in the liver, such as those that Dr. Howland has brought about by delayed chloroform poisoning.

In 1906 and 1907 Ewing and I published two papers on the clinical significance of the urinary nitrogen, as applied more particularly to the examination and diagnosis of conditions such as the toxemia of pregnancy, in which the liver on microscopical examination shows changes somewhat comparable to those found in chloroform poisoning. The main feature of this investigation was that changes in the distribution of the nitrogen were indicative of changes in the organs leading to the formation of the end products of metabolism. There were laid down certain standards for the distribution of the nitrogen, outside of which findings might be considered pathological.

I have not assured myself that the method as generally used has given altogether satisfactory results. The reason for this is a consideration of results similar to those of Dr. Howland, and the further conclusion that much more information must be available on the behavior of normal persons on restricted diets and with different states of nutrition.

By reason of the technical difficulties in procuring subjects for such investigations, I have been obliged to experiment with animals; but the results which I have thus obtained have convinced me of the necessity for a complete investigation of normal metabolism in undernutrition, before the method of nitro-



gen partition can be used for the purposes of accurate diagnosis. Work which I have finished on the hourly excretion of urine has shown that it is possible to obtain from the same subject, on the same day, samples of urine simply astonishing in their differences in composition; and that the change from one composition to another takes place with the greatest rapidity.

I have spoken first of the negative results of Dr. Howland's investigation. I wish now to call attention to certain positive results which he has obtained which seem to be of great interest.

In a Harvey lecture given about a year ago, Folin emphasized a direction which he considered was of the highest importance for investigation into pathological metabolism. This was the study of those processes which are connected with the essential carrying out of protein metabolism, quite apart from any question of food intake. To this type of metabolism the name "nitrogenous" has been given. One of these processes apparently leads to the formation of creatinin; and if creatinin be absent, one would conclude that this function, an essential one for the organism, has been abolished. In one of the cases which Dr. Howland has presented, creatinin is shown, for the first time in any urine so far as my knowledge goes, to be absent. I should conclude from this a very profound disturbance, probably irrecoverable, as a result of chloroform poisoning. In all his cases there is a marked diminution in the amount of creatinin eliminated, as a result of the toxic process.

This is one of the constant results which I have met with in brombenzol, hydrocyanic acid, carbon monoxid, and chloral hydrate intoxications, and has also been seen by Shaffer and others in certain pathological conditions in man. That it is not due simply to starvation I can show by a comparison of a number of experiments which I have made with normal fasting animals, and we must accept the low creatinin in Dr. Howland's results as a distinctly pathological indication of importance.

With regard to the rise in creatin, we have also, as Folin pointed out, an index which is probably of great significance. In my fasting animals which have been mentioned, creatin appears



on the third or fourth day, depending probably on the condition of nutrition of the animals. With, however, the administration of brombenzol, hydrocyanic acids, carbon monoxid, or chloral hydrate, the excretion of creatin is increased far beyond anything I have ever observed in fasting. On the other hand, I have never found the most unusual amounts of creatin which Dr. Howland has obtained, and I conclude, therefore, that the process of chloroform poisoning is one of most severe character on this account.

I have not taken up the distribution of sulphur, nor its importance in diagnosis. The matter seems to me at present much too obscure to use as a basis for diagnostic work, as Zweifel has attempted. It is, however, interesting, as Dr. Howland has pointed out, that the type of protein attacked is one containing a large proportion of sulphur. This I have found in brombenzol poisoning and in hydrocyanic acid. That a protein of this kind is very important for the individual is shown in undernutrition. Here I have found that while the animal parts with its nitrogen readily, it seeks to protect its sulphur, so that during a period of undernutrition much more nitrogen is lost than sulphur. Precisely the opposite occurs in chloroform poisoning, hence the toxic action of the drug. The important high sulphur protein is katabolized, and this most probably increases the poisonous effect of the anesthetic.

DR. E. LIBMAN said that he thought the Societies should be very much pleased with the opportunity which they had had to listen to so valuable a paper, both because the subject had been so well worked up, and because it was an unusually good subject for a joint meeting. He agreed with Dr. Ewing that these cases were not infrequent, particularly the milder forms. Of course, the danger now would be that everything would be attributed to chloroform poisoning, but at any rate it was clear that there was great danger in using chloroform. He wished to record his impression that alcoholics were more likely to suffer from delayed chloroform poisoning.

## A CASE OF CONGENITAL FALSE DIAPHRAGMATIC HERNIA.

H. S. MARTLAND, M.D.

The specimens which I have to show comprise the thoracic viscera of a man who died as the result of a congenital deficiency in the central tendon of the diaphragm, which opening connected directly with the pericardial cavity, the heart at autopsy being surrounded by the entire transverse colon, with the great omentum and the greater part of the splenic and hepatic flexures of the gut.

The patient was a man, seventy years of age, who was admitted to the Newark City Hospital in December, 1908, suffering from intense dyspnea, which he had had for about one week. His family and personal history, except for the fact that he was never confined to his bed on account of sickness, had no bearing on the condition to be described.

On admission, the patient presented the clinical picture of an acute right heart dilatation, being markedly cyanotic and dyspneic, with rapid, irregular, and feeble pulse. Aside from these symptoms, there was little in his physical examination which was of interest.

The apical cardiac impulse could not be seen nor felt, but was heard best in the sixth intercostal space in the left mid-clavicular line. The heart sounds were weak and distant, no murmurs being heard. Examination of the lungs revealed crepitant and subcrepitant rales in both infraclavicular spaces, and large moist rales over both bases posteriorly. The abdomen was negative. Examination of the urine showed a moderate amount of albumin, a few small hyalin and granular casts, and a specific gravity of 1.016.

The treatment consisted of the usual cardiac stimulants, but the patient's condition did not improve and he died seventeen hours after admission.

On autopsy the condition shown in the photograph was found. On opening the abdomen, the small intestine occupied

the usual position. The serosa showed in three places, at intervals of about 20 to 30 cm., large injected vessels and a red-dened and thickened peritoneum. These areas were practically all in the jejunum, and were thought to be areas of chronic hemorrhagic peritonitis. The transverse colon and great omentum were conspicuous by their absence. The rest of the abdominal viscera were all in their normal positions.



The right dome of the diaphragm reached the fourth interspace, the left was opposite the fifth rib. Just above the left lobe of the liver, the hand could be passed through a large oval opening, 4 x 5 cm. in diameter, directly into the pericardial cavity, where the heart was felt surrounded by the distended transverse colon and the great omentum. On gently dragging on the splenic flexure of the colon, the hernia could be easily reduced as far as the middle of the transverse mesocolon, where there was a small area of gastrocolic omentum adherent to the right free edge of the opening.

The stomach was in the abdominal cavity, somewhat

turned, a portion of its posterior surface presenting, the greater curvature just entering the hernial opening.

On opening the pericardium, the parietal layer was diffusely but only moderately thickened. The right heart was dilated; the left ventricle was firmly contracted. The hernial opening presented rounded borders, and the peritoneum of the under surface of the diaphragm was continuous with the parietal pericardium. There was no hernial sac; nor was any evidence found of a former suppurative pericarditis, empyema of the pleural cavities, suppurative hepatitis, subphrenic abscess, ulcer of the stomach, or neoplastic growth near the diaphragm.

The remainder of the autopsy showed only the ordinary visceral changes of senility. The left adrenal, however, presented a cortical adenoma, about 25 mm. in diameter. It was concluded, therefore, that death was due to cardiac embarrassment, due either to a slipping of too large a portion of intestine, or to gaseous dilatation of the same, through a congenital deficiency of the diaphragm in this position. From the chronic inflammation seen in the small intestine, it seemed probable that this portion also had at times slipped through the hernial opening.

An explanation of this congenital deficiency upon an embryological basis was rather difficult, although it might be included under the theory of diaphragmatic hernia in general; namely, that the partition subdividing the primitive body cavity into pleuro-pericardial and peritoneal compartments is completed by fusion of segments (septum transversum, pillars of Uskow) which for a time are separate; arrested development or delayed union therefore results in abnormal clefts, and it is evident that various degrees of developmental arrest or delayed union may produce corresponding imperfections in the future diaphragm. In this case such an arrest probably took place at about the fifth or sixth week of embryonal life. It was probable also that this was a teratological rather than an embryonal fault, and one which was closely allied to a beginning subthoracic ectopia cordis.

## ON THE VALUE OF THE USE OF AMMONIUM OXALATE IN BLOOD CULTURE TECHNIQUE.

CHARLES RYTTEBERG, M.D.

The value of blood cultures as a diagnostic method has become more and more evident in recent years. With the progress of investigations along this line, it has been found necessary to use different methods for different types of cases, and in the course of the work a large variety of media has been introduced. In the ordinary blood culture it is often advisable to use four or more media.<sup>1</sup> In hospitals it is easier to use a variety of media, but in private practice this is not so simple. Epstein<sup>2</sup> suggests the use of ammonium oxalate in blood culture work for the purpose of preventing coagulation of the blood, so that the use of elaborate media at the bedside could be dispensed with and a number of methods could be employed with the blood culture after it had reached the laboratory. He pointed out in his paper that, apart from this advantage, it allowed of a more careful distribution of the blood in the various media. It has been the experience of all investigators who have made blood culture studies, that it is difficult to distribute rapidly and properly in various media blood that is on the point of coagulation. He also pointed out that the coagulation of the blood adds to the bactericidal action of the serum. Chantemesse, in his work on typhoid blood cultures, reported the use of sodium citrate to prevent coagulation of the blood. Two months before the issue of the paper by Chantemesse, the ammonium oxalate method was introduced into our laboratory.

It is evident that there is an additional advantage in the use of ammonium oxalate, in that the blood can be obtained from the patient by a person who is not thoroughly conversant with bacteriological technique. And it is also an advantage in private practice to have a method which prevents as much as possible the alarm of the patient or the relatives by the display

<sup>1</sup>LIBMAN: *Johns Hopkins Hosp. Bull.*, July, 1906.

<sup>2</sup>EPSTEIN: *Amer. Jour. of Med. Sciences*, September, 1907.



of a large amount of apparatus. It is apparent that oxalated blood can be centrifugalized, and that spreads can then be made from the sediment and examined microscopically for bacteria in intense infections. The supernatant fluid can be employed for the determination of the opsonic index.

In the *Mount Sinai Hospital Reports*, Volume V, I have already given our experience with the use of ammonium oxalate solution in ninety cases. In the present paper I shall give the result of our studies up to March 15 of the past year. The present series includes the cases given in the previous paper.

The following reagent, devised by Epstein, has been employed in our investigations:

Ammonium oxalate, 2 gms.  
Sodium chloride, 6 gms.  
Aq. dest., 1,000 c. c.

The resulting solution is distributed into large test tubes in quantities of ten c. c. (measured accurately by means of a pipette or measuring funnel), and sterilized for twenty minutes on each of three successive days. It can be seen by referring to the formula that this is an isotonic solution, for it contains 0.6 per cent. sodium chloride. The level of the fluid is indicated on the tube by a blue pencil mark, which serves as a control over evaporation and shows at a glance the approximate amount of dilution of the blood after it has been added to the solution. The tubes are then stored in the ice-box until they are needed. The oxalate solution should never be used immediately after being taken from the ice-box, but should be allowed to stand at room temperature for some time, or gently warmed. The cold solution might exert a detrimental effect on the organism sought, and by eliminating this factor, the chances of a negative result are diminished. Our experience has shown us that a fresh solution is preferable, so that our stock is renewed every third or fourth week.

Briefly stated, the action of the oxalate is as follows: It precipitates the calcium salts of the blood in the form of calcium oxalate, thereby preventing the coagulation that would

normally occur. In other words, it is a decalcifying agent, and by removing the calcium base the fibrin ferment of the withdrawn blood is rendered inert, and hence clotting does not take place.

*Technique of Obtaining Blood and Preventing Coagulation.*—We employ the usual apparatus and method for obtaining the blood, preferably from one of the veins in front of the elbow. In our investigations part of the blood (usually 4 to 8 c. c.) was immediately introduced into the tube of the oxalate solution, after sterilization of the mouth of the tube in the flame of an alcohol lamp. The remainder was distributed in the usual series of media. The 10 c. c. of ammonium oxalate are more than sufficient to decalcify 10 c. c. of blood, which was the maximum amount used in any single case because of the danger of contamination in case the blood oxalate solution came into contact with the cotton plug. Gently oscillating the tube is sufficient to mix the blood thoroughly with the oxalate solution in cases where a moderate amount (2 to 5 c. c.) of blood has been obtained. When 6 to 10 c. c. are introduced into a single tube of the oxalate solution, it has been my technique to pour the mixture into a sterile tube and back again into the original tube with the usual precautions. In this way one can be sure of a more rapid and even distribution of the blood in the oxalate solution, so that all possibility of clotting is obviated, even though the coagulation time of the patient's blood be markedly diminished. On standing, the blood-oxalate solution usually separates into a stratum of blood cells with a supernatant layer of turbid fluid. When later platings are made, it is desirable to pour the mixture into a sterile tube and back again into original tube before adding the oxalated blood to the medium selected. This distributes the cells evenly in the solution, and plates of uniform color are obtained.

*Media Used.*—In our investigations the routine blood culture set employed in our laboratory was used as a control. This set was introduced by Dr. Libman, and consists in the use of flasks of plain bouillon (1 per cent. acid) and 2 per cent. glu-

cose broth bouillon (1 per cent. acid), together with plates poured from the blood mixed with plain agar (1 per cent. acid), serum agar, 2 per cent. glucose agar, 2 per cent. glucose serum agar, 5 per cent. glycerin agar, and neutral plain agar. Corresponding flasks and plates from the oxalated blood were made from time to time, some at once, others at intervals of thirty minutes, one, two, three, or five hours, etc., depending upon the amount of blood withdrawn. Occasionally we have extended the intervals, plates at times being poured twenty-four to thirty-six hours after the blood had been obtained. In the intervals between plating, the oxalated blood was kept in the thermostat at 37° C.

*Results.*—Three hundred and twenty-four blood cultures have been taken in which the method has received a fair trial. Of this number, eighty-seven positive cultures are available for study. The blood cultures were made in all the usual types of disease encountered in hospital work. The following is a short list of the diseases in which the positive results were obtained: Typhoid fever, pneumonia, post-partum infections, pyelitis, pyosalpinx, infectious endocarditis, otitic infections, erysipelas, local infections in various parts of the body, abscesses of various parts of the body, gall-bladder infections, osteomyelitis of various bones, glanders, and general cryptogenetic infections.

The main point of the study has been to determine the effect of the ammonium oxalate solution upon infected blood. Is this effect deleterious or not? In analyzing our results, many factors must be taken into consideration. A few of the more important ones which will be taken up are the number of organisms in infected blood in various pathological conditions; the viability of different bacteria; the bactericidal effect of the serum introduced into the oxalate solution; the physical appearances of media inoculated with oxalated blood.

*Number of Organisms in Infected Blood.*—Typhoid fever is a disease associated with relatively few organisms in the circulating blood. Twenty-six positive cultures in this series, representing 190 c. c. of blood, show a total of 172 colonies, an

average of less than one colony per c. c. of blood. Of these twenty-six cultures the highest single count was about three colonies per c. c.; the lowest, one colony from 10 c. c. of blood. The length of time that the disease has lasted seems to be of some consequence, more bacilli being found per c. c. in the earlier stages or relapses than late in the disease. Against the possible objection that the small number of organisms is consequent upon the bactericidal effect of the blood, is the fact that these organisms multiply in defibrinated, oxalated, laked, and clotted blood without the addition of any nutrient medium, as pointed out by Epstein.<sup>1</sup>

One can readily appreciate that in a given sample of blood containing very few organisms or a single bacillus, there is a large element of chance as to whether a medium of the oxalate series or of the control will be favored. In twenty-five cultures in which both methods were used, twenty-one showed growth in some media of each set. Of the remaining four cultures, two showed growth in a single flask of the control series; one was positive in the Conradi medium and a flask of bouillon; and one showed a single colony on a plate and growth in a flask. To offset these four cases, the oxalate method alone was employed on four occasions; each gave a positive result. It is therefore reasonable to suppose that, had all of the blood obtained in the four cases first referred to been introduced into the ammonium oxalate solution, subsequent platings would have shown growth. Apparently that portion of blood used in the oxalate series in these four cases contained no bacilli, and hence the media employed remained sterile.

To emphasize still further the element of chance in transient blood infections and bacteriemias associated with few bacilli, four cases in our series of streptococcemias may be mentioned. Two showed a single colony or a positive flask in the control, the oxalate series remaining negative. Of the other two, one showed three colonies on the plate of the oxalate series, the control media being negative; the other gave a positive

<sup>1</sup>EPSTEIN: *Amer. Jour. of Med. Sciences*, August, 1908.

result in a flask and plate of the oxalate series, four plates and a flask of the control being sterile. Had all of the blood obtained been introduced directly into the oxalate solution, instead of only a portion, the first two cases would have undoubtedly shown growth in the platings. Most of our streptococcus infections recorded in this series have been very intense, and there has been no difficulty or discrepancies encountered in comparing the two methods. A rough average of the cases of post-partum infections shows about sixty colonies per cubic centimeter of blood. Between the two extremes represented by the few bacilli of the typhoid bacteremia and the overwhelming number in some post-partum infections—at times 500 to 900 to the cubic centimeter—all of the other blood infections can be numerically grouped. It has naturally been easier to study the value of the oxalate method in those cases where many organisms were present than when the reverse held true.

*Viability of Different Bacteria in the Solution.*—This factor is not a negligible one. Most organisms isolated from the blood can be made to grow without difficulty, such, for example, as the typhoid bacillus, *Bacterium coli*, *Bacillus mucosus capsulatus*, *Micrococcus aureus*, and many strains of streptococci and pneumococci. On the other hand, there are various organisms, like atypical pneumococci, the attenuated streptococci associated with endocarditic lesions, and, possibly, the meningococcus and gonococcus, which require extreme care in isolation. The last mentioned organisms we have not encountered in the series under consideration. In general, one has some idea of the identity of the possible infecting agent from the history of the case. Therefore, he can select the most favorable media before distributing the oxalated blood. If this be done, there need be no doubt in most cases concerning a negative finding.

Although our experience with the attenuated organisms found in certain cases of endocarditis has been limited, we have recovered them from the blood oxalate solution in several cases. The attenuated streptococcus grows extremely poorly or not at



all, even on the most favorable media. The studies in the use of ammonium oxalate in cases of subacute and chronic streptococci endocarditis will be published later, when enough cases have been studied.

*Bactericidal Effect of Serum Introduced into Oxalate Solution.*—The work of Eppenstein and Korte indicates that the typhoid bacillus develops an immunity against the bactericidal action of the blood of the host. Epstein has confirmed this fact. *Bacterium coli*, *Bacillus mucosus capsulatus*, most streptococci and pneumococci, *Bacillus mallei*, *Micrococcus aureus* and *Micrococcus albus* are apparently not inhibited by any bactericidal effect of the serum, but tend to multiply in the oxalate solution. Concerning the possible bactericidal effect, we adopted the rough test of inoculating sterile oxalated blood from negative cultures with various organisms. In no instance was a later sub-inoculation from the oxalated blood sterile; in fact, we often employed this method for increasing viability and improving growth in dealing with attenuated organisms. Whether there was originally a bactericidal effect in the fresh blood or not is of no importance here; if it was present it may have been neutralized chemically or by dilution in the ammonium oxalate solution.

In only one instance was there any question as to the exertion of a possible bactericidal effect. This was a case of pneumonia complicating chronic endocarditis. The control media showed an average per cubic centimeter of blood of 4,750 colonies; the oxalate plates (2), which were poured twenty hours after the blood had been obtained, showed only 106 colonies per cubic centimeter of blood. Insufficient blood had been obtained for extended observations, and through a misunderstanding the plates from the oxalated blood were not poured after intervals of one and two hours, as had been intended. Unfortunately, the death of the patient precluded further investigation, so that observations as to the behavior of this particular sample of infected blood over the period up to the twenty-four hour plating, were not possible. While this case is of in-

terest, it does not reflect upon the method; it will be the exception rather than the rule, when the interval between the time the blood is obtained and the time it reaches the laboratory is more than two or three hours.

While conceding a possible bactericidal effect in this particular instance, although the same is quite unlikely, the patient being moribund at the time the blood was obtained, I was, nevertheless, able to recover ample organisms after the twenty-four hour interval to permit of easy diagnosis. This was the only doubtful case; eight others in which the pneumococcus was identified showed either a corresponding number of colonies in the oxalate series as compared to the control, or an increase.

*Appearance of Media Inoculated with Oxalated Blood.*—Plates properly poured from the blood-oxalate solution after admixture with any nutrient medium present no macroscopic difference from plates poured in the usual way. Briefly summarized, the following data can be regarded as reliable: The phenomena of hemolysis, as produced by the streptococcus, and often by the *Micrococcus aureus*, are in no way interefered with by the ammonium oxalate solution. Likewise, the appearance of the typhoid "type colony"<sup>1</sup> on the 2 per cent. glucose agar plates of the oxalate series is identical with that on the control plates of the same medium. With the pneumococcus, we have observed hemolysis on some media, and zones of green coloration surrounding the colonies; on others, analogous plates in the two methods presenting identical features. With *Bacillus mucosus capsulatus*, observations on glucose agar plates as regards the production of zones of green coloration about the deep colonies, and later zones of precipitation, indicate that corresponding phenomena are displayed in the two methods. It is therefore reasonable to assume that with other organisms we may expect to find that the oxalate method will show features in no way different from those seen in blood media poured in the usual way.

*Organisms Studied.*—The following is the summary of

<sup>1</sup>EPSTEIN: *Proceedings of the New York Pathological Society*, Oct., 1906.

bacteria isolated from eighty-seven positive blood cultures since the oxalate method was introduced:

Bacillus typhosus .....	29
Streptococcus .....	26
Pneumococcus .....	9
Bacillus mucosus capsulatus .....	7
Streptococcus mucosus capsulatus .....	1
Micrococcus aureus .....	5
Bacterium coli .....	1
Bacillus mallei .....	2
Attenuated streptococcus .....	2
Bacillus proteus (atypical).....	1
Micrococcus albus .....	1
Micrococcus zymogenes .....	1
Mixed infection .....	2

*Effect of Ammonium Oxalate Solution on Various Organisms.*—In our study of typhoid infection, it was not uncommon to note an increase in the number of colonies on the glucose plates poured from the oxalated blood.

The streptococcus tends, in most instances, to multiply rapidly in the oxalate solution, the increase at times being several hundred-fold.

While the pneumococcus does not show as marked a multiplication as the streptococcus, in our nine positive infections there was evidence of increase in number of colonies in the majority of instances.

The Micrococcus aureus also tends to multiply in the oxalate solution; the same may be said of Bacterium coli and the Bacillus mucosus capsulatus.

We were fortunate in having for study two blood cultures in two cases of glanders. In the first case there was an increase noted in the number of bacilli, while in the oxalate solution. In the second culture the oxalate series showed fewer colonies, probably due to chance.

In investigating an atypical case of pneumonia the Streptococcus mucosus capsulatus was isolated, the result in the oxalate method was good.

Studies of attenuated streptococci found in cases of sub-

acute endocarditis will be published later. It can be stated here simply that our work thus far indicates that the ammonium oxalate method is satisfactory in such cases.

The *Micrococcus albus*, *Micrococcus aureus*, and *Bacillus proteus* were each studied once. In every instance the organism was readily recovered from the oxalate solution.

The post-mortem blood cultures are of interest. One was a case of suppurative cholangitis from which *Bacterium coli* was isolated during life; the post-mortem culture showed this organism together with the streptococcus. The other culture taken after death showed three organisms on the plates: *Bacterium coli*, *Micrococcus aureus*, and a streptococcus. From these two cases it may be deduced that the oxalate solution will be as serviceable in mixed infections as in the bacteriemias due to a single organism.

*Spreads Made from Centrifugalized Oxalated Blood.*—In the severe infections a clue to the case may be furnished early by such spreads. We have had some success in these examinations, especially where the streptococcus, pneumococcus, and *Micrococcus aureus* were the infecting organisms. In the bacteriemias associated with relatively few organisms, e. g., typhoid fever, the examination is necessarily useless.

### *Conclusions.*

Our experience, as detailed above, leads us to believe that it is safe to use the ammonium oxalate method as an intermediate step in blood culture technique. We have shown that good results were obtained with all of the organisms that were encountered during the course of the study. Unfortunately, the meningococcus, gonococcus, and paratyphoid bacilli were not met with, and the *Streptococcus mucosus capsulatus* was encountered only once.<sup>1</sup> In the study of mixed infections no difficulty

<sup>1</sup>Any experiences which we may have in connection with these organisms will be published later, as will also a comparative study of the value of ammonium oxalate and sodium citrate. Our present experience is decidedly in favor of the former.

should be experienced if the distribution of the oxalated blood is made as soon as the material arrives at the laboratory. The simple method suggested by Epstein as an intermediate step in blood culture work should lead to the more general use in private practice of blood cultures as a diagnostic method.

---

## A STUDY OF THE PATHOLOGICAL ANATOMY OF THE PANCREAS IN NINETY CASES OF DIABETES MELLITUS.

RUSSELL L. CECIL, M.D.

Study of anatomical changes in diabetes mellitus has been limited almost exclusively to lesions which occur in the pancreas. In 1889 were published the well-known experiments of von Mering and Minkowski (1), in which they showed that the removal of the pancreas in dogs produced typical diabetes. The diabetes of depancreatized dogs has suggested that the pancreas furnishes an internal secretion which controls carbohydrate metabolism. Since the other organs of internal secretion are ductless glands, the islands of Langerhans, the only parenchymatous tissue in the pancreas not in communication with the ducts, were associated with pancreatic internal secretion (Laguesse (2), Schafer (3)) at a time when evidence of this association was wanting.

Opie (4), in 1900, described definite pathological changes in the islands of Langerhans in diabetes. These changes consisted most frequently in increase of fibrous tissue within and about the islands. In other cases of diabetes Opie found hyaline degeneration of the islands of Langerhans, occasionally in a pancreas otherwise entirely normal. Opie reaches the conclusion that where diabetes is caused by a lesion of the pancreas, the lesion is of such a character as to injure or destroy the islands of Langerhans. These studies have been followed by a



large number of articles upon the same subject, and some observers have supported, while others have opposed his views. In addition to the lesions described by Opie, other changes in the islands of Langerhans have been noted in association with diabetes mellitus. Schmidt (5) found acute inflammation limited to the interacinar islands in a child ten years old. Ssobolew (6) and others have reported absence of the islands of Langerhans, or great diminution in their number. Hypertrophy of these islands, associated with a peculiar adenoma-like arrangement of their cells, has been described by Reitmann (7), Herxheimer (8), MacCallum (9) and others.

Sauerbeck (10) in 1902 collected from various sources one hundred and seventy-six cases of diabetes in which the condition of the islands had been noted. He found that lesions in the islands of Langerhans had been observed in sixty-two per cent. of the cases.

The present work was undertaken at the suggestion of Dr. Opie, with the hope that the study of a large number of cases by a single observer might furnish accurate information concerning the condition of the pancreas and of the islands of Langerhans in diabetes mellitus. So far as I know, only two of the following cases have been previously reported.

*Gross Pathology of the Pancreas in Diabetes.*—Of my cases, the pancreas has been described as small or atrophic in only twenty-five per cent. With the exception of this diminution in size, the pancreas exhibited very few notable macroscopic changes. The weight has been given in thirty-six cases, and ranges from thirty to one hundred and eighty-five grammes. The average weight was ninety-four grammes. This is scarcely less than the weight of the normal pancreas, which averages, according to Vierordt, ninety-seven grammes.

In considering the histological pathology of the pancreas in diabetes, it will be convenient to divide the subject into three parts: (1) Changes in the interstitial tissue. (2) Changes in the glandular acini. (3) Changes in the islands of Langerhans.

*Changes in the Interstitial Tissue.*—Opie (4) has shown

that the interstitial changes which follow obstruction of the duct differ from those observed in connection with diabetes. In the former, sclerosis is chiefly interlobular, and while the lobules may be invaded to a greater or less extent by the newly formed tissue, the progress of the lesion is apparently inward from the periphery of the lobule. In the pancreatitis of diabetes, the reverse is true. The new growth originates between the acini, and interlobular sclerosis, if present at all, is a later phase of the process.

Of the ninety cases which I have studied, sixty-four, or seventy-one per cent., show a definite chronic interacinar pancreatitis. In twenty-one, or twenty-four per cent., the sclerosis is marked. The distribution of this new growth is generally uneven, some lobules being more involved than others. In a number of cases this "focal" sclerosis is conspicuous. Where the induration is advanced, many of the lobules have been largely replaced by fibrous tissue, while the glandular acini which still survive are compressed and distorted, and may give evidence of atrophy. Although the new formed fibrous tissue is often most conspicuous about the vessels and ducts, I have not been able to establish any constant relationship. In many cases, especially where the lesion is mild, the sclerosis seems more advanced in the neighborhood of the islands of Langerhans.

The relation of age to chronic interacinar inflammation is important. The lesion has been entirely absent in all of the four cases under twenty years of age. Between the ages of twenty and thirty, only twenty-five per cent. of cases show interacinar new growth. After thirty, interacinar sclerosis is the rule, being present in ninety per cent. of all cases.

Typical chronic inflammation of the interlobular variety has been observed in only four cases.

An extensive infiltration of lymphoid, eosinophile and plasma cells has been observed very frequently with both types of chronic interstitial pancreatitis. Of the sixty-four cases with interacinar pancreatitis, thirty have shown an abundant cellular infiltration. Lymphoid cells constitute the greater part of this

infiltration, but eosinophile cells and plasma cells are also plentiful. The presence of a considerable number of cellular elements in the stroma would seem to indicate that the inflammatory process was still in the active stage. Polymorphonuclear leucocytes were found in the stroma in greater or less numbers in eight cases, always associated with infiltration of lymphoid cells.

Considerable infiltration of the pancreatic stroma by adipose tissue was found in twenty-six of my cases. Three of these showed a very marked invasion, the lobules as well as many of the acini being widely separated by fatty tissue. In these three cases, the parenchyma appeared much reduced in amount and the sections gave the impression that many acini had been replaced by adipose tissue.

Arteriosclerosis, it is well known, accompanies a large percentage of cases of diabetes. Of my cases, eighty per cent. showed a thickening of the wall of the pancreatic vessels and in half of these cases the vessels were also hyaline. The small arterioles seem to show this change first, and in many instances the lumen of the smaller vessel has been almost entirely obliterated by hyperplasia of the medial coat. Hyaline changes were, moreover, more commonly observed in the small than in the large vessels.

The incidence of arteriosclerosis in diabetes increases rapidly with age. In my series it was present in only forty per cent. of the cases between twenty and thirty years of age, increased to seventy-seven per cent. in cases between thirty and forty, and was present in all but two cases occurring after the fortieth year.

*Changes in the Secreting Parenchyma.*—Clinically and experimentally, cases are constantly encountered which give no evidence of a disturbance in carbohydrate metabolism, although they show at autopsy extensive destruction of the glandular acini. According to my observations, the most common change of the acini with diabetes is the compression and atrophy, seen in association with the severer types of chronic interacinar pancreatitis. An acinus which has undergone this change is smaller

than the normal; its constituent cells are pressed together and individual cells are ill defined; in some acini a number of the cells have already been destroyed, so that only a part of the original acinus remains. Many acini have been completely obliterated and their place is taken by connective tissue.

*Changes in the Islands of Langerhans.*—In the ninety cases which I have studied, seventy-nine, or eighty-eight per cent., have shown definite anatomical changes in the islands. By far the commonest lesion was fibrosis, which was observed in seventy-six cases. In forty it was moderate; in thirty-six advanced. In the former cases the islands are surrounded by capsules of fibrous tissue which are thicker than the normal, almost invisible sheaths. The fibrillary coating of the insular capillaries is also definitely increased in thickness, converting the vessels into coarse septa which extend in from the capsule and anastomose at the center of the interacinar island. The cells forming the columns show little or no change in number or appearance.

In the second group of cases the lesions are of a similar nature, but more advanced. The islands of Langerhans are imbedded in dense fibrous tissue which separates them widely from the surrounding alveoli. The intransular sclerosis still follows the path of the insular capillaries, the walls of which are several times thicker than the normal. Sections through the center of the body will show an extensive patch of dense fibrous material, rich in spindle cells and sending out broad septa towards the periphery. The cells of the islands are often reduced in number, and appear small and compressed. Occasionally an island of Langerhans is found which has been almost completely converted into fibrous tissue.

Insular sclerosis of the mild type is usually associated with a moderate chronic interacinar pancreatitis, but this relation is not present in all cases. In four of my cases where there was no evidence of a chronic interstitial inflammation, a definite increase of connective tissue was found in the interacinar islands. In these four cases the age varied from twenty-six to seventy

years. Advanced sclerosis of the islands of Langerhans was always associated with considerable interacinar sclerosis, and the insular lesion was always most severe in those areas where the induration was most marked.

The relationship between sclerosis of the islands of Langerhans and arteriosclerosis is of interest. Fibrous changes in the islands are, with few exceptions, associated with a sclerosis of the smaller pancreatic arterioles. Of my cases of insular sclerosis, all but five showed thickening of the vessel walls; in these five cases, no arterial sclerosis was recognizable. Sclerosis of the islands of Langerhans in its early stages is probably a part of more or less generalized arteriosclerosis. It doubtless affects the capillaries of the islands of Langerhans or their afferent vessels and in this respect resembles the beginning fibrous changes in the glomeruli of the kidney. When the process is advanced, chronic interacinar inflammation is always present and the entire interstitial framework of the island becomes involved in the new growth. The insular capillaries, however, still bear the brunt of the attack.

Hyaline degeneration of the islands of Langerhans is the lesion which has occurred next in frequency to sclerosis, being present in twenty-seven cases (thirty per cent.). In most instances it has been associated with sclerosis of the pancreatic vessels and of the islands of Langerhans. In six cases with hyaline changes in the interacinar islands there was no increase in the interacinar connective tissue. As a rule the majority of the islands of Langerhans were affected, but in a few cases only an occasional island showed the change. The hyaline material is first deposited along the capillaries of the island, separating the latter from the cells. As the process advances, it extends outward. Many of the cells are replaced by the hyaline substance, and those which still survive are often compressed and atrophic. Eventually, the entire area of the island may be occupied by homogeneous hyaline material. The nuclei of the endothelial cells appear to persist longest, but finally these, too, are destroyed.



I have found hyaline degeneration of the islands of Langerhans in only two of the cases under thirty years of age. It appears to be most common after the fifth decade. In my cases I have found that this lesion was, with the exception of one case, always associated with diabetes of more than one year's duration. The average duration of the diabetes in sixteen cases with hyaline islands was three years and six months.

In nine cases I have observed a well-marked infiltration of leucocytes about the islands of Langerhans. A more or less general infiltration of the same character sometimes accompanied this lesion, but the cells were more numerous and concentrated in the vicinity of the interacinar islands. The cells were generally arranged in the form of a halo about the island of Langerhans just outside of the capsule, though in some cases the island itself was invaded. The average duration of the diabetes in the six cases of this group where the duration was definitely stated was only eleven months.

*Hypertrophy of the Islands of Langerhans.*—Laguesse (2) found that the islands of Langerhans in the normal pancreas of man varied from one hundred to four hundred microns in diameter. Islands of Langerhans exceeding four hundred microns were very rare. Lydia Dewitt (11) measured these bodies in the human pancreas, and found that they averaged .0153 c.mm. in volume. In her measurements the diameter never reached 400 microns. The pancreas in thirty-eight per cent. of my cases showed islands of Langerhans which equalled or exceeded 400 microns in diameter. Round or ovoid islands were selected and the long diameter was measured.

In one case an island of Langerhans was found which measured seven or eight hundred micromillimeters—a diameter about four times that of normal. In the cases where giant islands were found, the average size of the interacinar islands was increased. Hyaline degeneration of the islands was associated with about a third of the cases with hypertrophy and it was observed that hypertrophied islands, as a rule, were free from hyaline material, or contained it in only small amounts.

Reitmann (7), Herxheimer (8), MacCallum (9) and others have described a peculiar form of hypertrophy of the inter-acinar islands, which they have encountered in the pancreas of some cases of diabetes. The cells displayed, instead of their usual arrangement in irregular cords or masses, a definite columnar arrangement, and were often grouped together in circular cords about capillaries. In seven of our cases, a similar lesion has been observed. The islands of Langerhans are considerably larger than the normal, some of them reaching a diameter of seven or eight hundred microns. Their contour is quite irregular; loops and cords of columnar epithelial cells push their way out between the adjacent acini, and, but for differences in staining reaction, might possibly be mistaken for normal glandular structure. In six of these cases, hypertrophy of the islands of Langerhans was associated with increase of fibrous tissue about the insular capillaries.

*Diminution* in the number of islands of Langerhans was a common finding. While there was no instance in my series of a pancreas entirely devoid of islands of Langerhans there were a number of specimens in which they were exceedingly few.

Several writers have found an absence or scarcity of islands in diabetes. Ssobolew (6) reported fifteen cases in which the islands were either absent altogether or were much diminished in number. Two factors probably contribute to explain this diminution. First, there is a group of cases in which the pancreas may show little or no change, and where the condition is perhaps due to a congenital defect. Opie reports the case of a child, fourteen years old, with hereditary diabetes, in which the number of islands showed a well-marked diminution. In a second group of cases, the scarcity of islands of Langerhans is associated with chronic interacinar pancreatitis of severe type. Here the islands are probably destroyed and their places occupied by fibrous tissue.

In twenty of my cases the islands of Langerhans showed a marked diminution in number, recognizable by inspection of sections. These cases may be classified as follows: (1) Scarcity

of islands in a normal pancreas (5 cases); (2) Scarcity of islands in association with chronic interacinar pancreatitis (15 cases).

*Cases in Which the Pancreas was Normal.*—Eleven of my cases showed no discoverable anatomical lesion in the pancreas. The pancreas in two cases of this group was described as small, but in all other respects the gross appearance agreed with the microscopic in suggesting no pathological changes. In five cases diminution in the number of interacinar islands was marked. The islands were of small size in five cases. The age in all but one of these cases was under thirty-five years.

*Relationship of Diabetes to Organs other than the Pancreas.*—*Cirrhosis of the liver* was present in seven of my cases. The pancreas from all of these cases showed well-marked chronic interacinar inflammation, which in two instances was far advanced. One etiological factor is probably active in both organs. The same statement is perhaps applicable to chronic nephritis, which was present in twenty-five cases, and was in all instances associated with more or less advanced chronic inflammation of the pancreas.

Two cases of cirrhosis of the liver were accompanied by *hemochromatosis*. This remarkable disturbance of iron metabolism was first described by von Recklinghausen (12), and is characterized by a deposition of a brown iron-containing pigment in the various tissues and organs of the body. Hemochromatosis with diabetes or "Bronzed diabetes" is well recognized. Von Recklinghausen found cirrhosis of the liver a constant feature of the disease, and more recently a number of writers have noted the occurrence of chronic interstitial pancreatitis.

Case XLII was obtained through the kindness of Dr. MacCallum of the Johns Hopkins Hospital. A man, thirty-seven years of age, gave a history of diabetes of nine months' duration. The urine contained 6.5 per cent. of glucose. Acetone and diacetic acid were also present. There were ascites and pigmentation of the skin. The patient died in coma. At autopsy, marked pigmentation was found in the liver, heart, pancreas, lymph glands and skin. The liver showed cirrhosis and the heart was hypertrophied. The

pancreas was large and firm and weighed 150 grams. On section it was brown, and mottled with fat. Microscopically, there is a very marked infiltration of fat tissue which appears to have replaced the glandular structures in many places. This invasion is not confined to the interlobular tissue, but separates the acini as well. There is also a definite new growth of connective tissue between the acini, which is rich in spindle cells and infiltrated with a moderate number of lymphoid and plasma cells. The interstitial tissue is the seat of an abundant deposition of light brown pigment which reacts positively to the chemical test for iron. Many of the acinar cells are loaded with this pigment. Some of the acini are considerably swollen, and their cells stain faintly. The walls of the blood vessels are not appreciably thickened.

The islands of Langerhans are very scarce, and considerably smaller than the normal, none of them measuring over 200 microns in diameter. The fibrous capsules about the islands are thickened, and infiltrated by pigment. Some of the island cells also contain pigment, but the remainder take their usual stain.

Case LIX was obtained through the kindness of Dr. Wright of the Massachusetts General Hospital. A man forty-five years of age had had three per cent. of glucose in his urine, as well as acetone and diacetic acid. The patient died in coma, and at autopsy there were found cirrhosis of the liver and pigmentation of the liver and pancreas. The pancreas was dark brown in color and rather soft.

Microscopically, sections from the pancreas show a marked new growth of connective tissue between the acini. The lobules are widely separated by adipose tissue. The stroma is the seat of a universal deposition of iron pigment which stains blue with ferrocyanid of potassium and hydrochloric acid. Many of the acinar cells are also loaded with pigment. The walls of the blood-vessels are somewhat thickened. Dense collections of lymphoid and polymorphonuclear cells are found in the neighborhood of the larger ducts. The islands of Langerhans are fairly numerous and normal in size, many of them are surrounded by dense capsules of fibrous tissue, and the insular capillaries are thickened. A considerable number of insular cells are distended with pigment, and give evidence of degeneration, the nuclei staining indistinctly.

The islands in these two cases show very similar lesions, namely, encapsulation by fibrous tissue and a deposition of iron pigment in the insular cells. In the case first described there was a marked diminution in the number of the islands of Langerhans, probably partly due to the advanced lipomatosis.

The association of diabetes with certain diseases of the ductless glands has been frequently observed. Hansemann (19) collected from the literature of the subject fifteen cases of ar-

*ophthalmic goiter* which had been accompanied by diabetes, but there had been no opportunity to study the pancreas. A number of other writers have more recently observed glycosuria in connection with Graves' disease. Falta, Eppinger and Budinger (16) have studied the relationship between the pancreas and the ductless glands,—more particularly the thyroid and suprarenal glands. By removing one or more of these organs and observing the effect in metabolism, they claim to have established a definite relation between the three organs.

I have been able to include in the present series one case of diabetes which was associated with exophthalmic goiter. The case was reported by Dr. Morris Manges in the *Mt. Sinai Hospital Reports*, Vol. II. Dr. Libman was kind enough to supply me with a part of the pancreas.

The patient, a woman, forty years of age, gave a history of diabetes of six months' duration, her chief complaint being weakness, emaciation and thirst. The urine contained five per cent. of glucose. Acidosis was present. There were marked exophthalmos, tachycardia and neuralgic pains. The latter were relieved by thyroid extract. Death occurred from asthenia and cardiac failure. At autopsy the thyroid gland was enlarged and firm; microscopically there were glandular hyperplasia and chronic inflammation. The pancreas was atrophic and weighed 45 grams; on section it was pale and soft.

Microscopically the pancreas exhibits typical chronic interacinar pancreatitis of advanced grade. The acini are small, and separated by dense fibrous tissue, which in some places has almost completely replaced the parenchyma. The stroma shows rich infiltration by lymphoid and plasma cells, with a few polymorphonuclear leucocytes. The vessel walls are thickened and hyaline. Islands of Langerhans are fairly numerous, but have small area. In places where the sclerosis is severe the interacinar islands are much involved, being buried in dense fibrous tissue and invaded by the same material. Many of them have been almost obliterated by the fibrous hyperplasia.

*Adenoma* of the thyroid gland has been noted in the anatomical diagnosis in two of my cases with diabetes (Cases XXIX and XXXIV). It is a significant fact in this connection that in both cases the adenoma-like hypertrophy of the islands of Langerhans, described above, is present. In Cases XXIX this hypertrophy affects nearly all the islands of Langerhans, which



often attain great size. In Case XXXIV the insular hypertrophy is also well marked. The pancreas in both of these cases shows a well-marked chronic interacinar inflammation with considerable increase of fibrous tissue in and about the islands of Langerhans.

*Myxedema* was found associated with diabetes in one of my cases (Case VI).

The patient, a woman, seventy-four years of age, was first admitted to the Presbyterian Hospital on March 12, 1899, complaining of weakness, shortness of breath, despondency, and gradual loss of mental powers.

There was a general thickening of the subcutaneous tissue. The skin was dry and scaly, and the nails and hair were brittle. There was puffiness under the eyes, and the tongue was thickened. Speech was deliberate and lisping in character. Pulse tension was high. At this time there was no glucose in the urine. The patient was treated with thyroid extract and improved rapidly.

A year and a half later, the patient was admitted again to the hospital complaining of thirst, polyuria, pruritus vulvæ and eczema. Myxedema was much improved. The urine contained four per cent. of glucose. The amount of sugar diminished under treatment. During the two years following, the patient was in the hospital several times, and finally died in coma September 6, 1902.

At autopsy the thyroid weighed only eight and a half grams; microscopically there is very advanced atrophy of the parenchyma. The alveoli have been almost completely obliterated and their places are occupied by fibrous tissue, densely infiltrated in places by lymphoid cells.

The pancreas weighed 120 grams, and was of tough consistency. Microscopically, advanced chronic interacinar inflammation, and universal infiltration of adipose tissue can be recognized in spite of extensive post-mortem digestion. The islands can be identified and show considerable sclerosis.

The occurrence of glycosuria with *acromegaly* has been observed in a considerable proportion of cases of this disease. Hansemann (19) and others have described such cases in which a chronic interstitial pancreatitis was found. Through the kindness of Dr. Norris I have been able to study the pancreas from a case of *acromegaly* which was accompanied by diabetes.

The case was reported by Dr. Norris in the *Proceedings of the New York Pathological Society*, February, 1907, and is the only case of *acromegaly* in which the condition of the islands has been described.

The patient, a man, thirty-three years old, was admitted to Bellevue Hospital with the following symptoms: Progressive enlargement of jaw, nose, ears, hands and feet. Persistent frontal headaches, and attacks of vertigo. Gradually increasing loss of vision, ending in atrophy of both optic nerves and almost complete blindness. There were recurrent epileptiform attacks. Glycosuria had been present during twenty-two months.

At autopsy, a large tumor was found, connected by a broad pedicle to the pituitary gland which was itself enlarged; microscopically, the tumor is composed of cuboidal or oval cells which are arranged in irregular alveoli. The stroma is very scanty. The alveoli are separated by capillaries, whose endothelial lining is apparently in direct contact with the alveolar cells. In some places the capillaries are dilated, giving the tumor a very vascular appearance.

The pancreas was large and firm, and weighed 170 grams. The lobulation was distinct and no macroscopic lesions were noted.

Microscopically, the pancreas is free from interstitial induration. There has been some post-mortem digestion in a few places, but otherwise the glandular acini are normal in appearance. The walls of the blood-vessels are slightly thickened. The islands of Langerhans are numerous, irregular in outline, and larger than the normal. One island is found which measures six hundred micromilimeters in diameter. Some of the larger islands present a very unusual appearance. The insular cells are large, and often columnar in shape and arrangement. In many instances the cords of cells form partial or complete circles, whose lumina contain the insular capillaries. These capillaries show definite sclerosis. There is a marked deposit of hyaline material in a few of the islands of Langerhans.

The coexistence of this adenoma-like hypertrophy of the islands of Langerhans with adenoma of the pituitary gland is especially significant if it be borne in mind that the same type of insular hypertrophy was observed in association with the two cases of adenoma of the thyroid gland; at present I can offer no satisfactory explanation of this association.

Other anatomical changes associated with diabetes are of considerable interest.

*Gangrene* is a common complication, and is generally attributed to two causes, arteriosclerosis and lowered resistance in the tissue, resulting from the diabetes. Gangrene occurred in sixteen of my cases and was in all instances associated with arteriosclerosis and well marked chronic interacinar pancreatitis.

In the present study of the pancreas from ninety cases of diabetes, the following pancreatic changes have been encountered:

1. Chronic Inflammation of the Pancreas.	
Interacinar pancreatitis, sclerosis of islands of Langerhans.....	39
Interlobular pancreatitis, sclerosis of islands of Langerhans.....	4
Interacinar pancreatitis, hyaline degeneration of islands of Langerhans .....	19
Interacinar pancreatitis with lipomatosis; sclerosis of islands of Langerhans .....	2
Interacinar pancreatitis, with lipomatosis, hyaline degeneration of islands of Langerhans .....	1
Interacinar pancreatitis, with siderosis of islands of Langerhans (Hemochromatosis) .....	2
2. Parenchyma normal; Lesions of the Islands of Langerhans.	
Sclerosis of the islands of Langerhans.....	4
Hyaline degeneration of the islands of Langerhans.....	7
Infiltration of leucocytes about islands of Langerhans.....	1
3. Pancreas normal .....	11
	—
	90

Of the eleven cases of normal pancreas, five showed a marked diminution in the number of islands of Langerhans. In two other cases the pancreas was abnormally small.

### *Conclusions.*

1. Anatomical lesions of the pancreas occur in more than seven-eighths of all cases of diabetes mellitus.

2. In diabetes associated with lesions of the pancreas, the islands of Langerhans constantly show pathological changes (sclerosis, hyaline degeneration, infiltration of leucocytes and hypertrophy).

3. In some cases of pancreatic diabetes (twelve of ninety cases) the lesion of the pancreas is limited to the islands of Langerhans.

4. In sixteen cases of diabetes associated with hyaline degeneration of the islands of Langerhans the average duration of the disease has been three and a half years. In six cases of diabetes associated with an infiltration of leucocytes about the islands of Langerhans the average duration has been eleven months.

5. Destructive lesions of the islands of Langerhans may be associated with compensatory hypertrophy of other interacinar islands.

6. Peculiar adenoma-like hypertrophy of the islands of Langerhans occurs in a small proportion of cases (seven of ninety) and may be associated with adenomata of the thyroid gland (two cases) and of the pituitary body (one case).

7. Diabetes mellitus occurring in association with hemochromatosis (bronzed diabetes) is referable to pigmentation and destruction of the islands of Langerhans.

8. The pancreas is found to exhibit no pathological changes in twelve per cent. of cases. In approximately one-half of these cases it has been noted that the size of the gland or the number of islands is much less than normal.

9. Fifty per cent. of cases of diabetes mellitus occurring before the age of thirty years are associated with lesions of the pancreas; seventy-five per cent. of all cases of diabetes in which the pancreas is normal occur before the age of thirty years; ninety-seven per cent. of cases of diabetes occurring after the age of thirty years are associated with lesions of the pancreas; and eighty-six per cent. occur in association with chronic interacinar pancreatitis accompanying arteriosclerosis.

10. Interacinar pancreatitis which occurs in seventy-three per cent. of all cases of diabetes is almost constantly associated with arteriosclerosis; gangrene of the extremities, which occurs with one-fourth of all cases of interacinar pancreatitis, is doubtless referable to the same cause.

11. Chronic interlobular pancreatitis, when associated with diabetes, is accompanied by sclerosis or hyaline degeneration of the islands of Langerhans.

12. Diabetes in association with myxedema or with exophthalmic goiter may be referable to a lesion of the pancreas, namely, chronic interacinar inflammation with sclerosis of the islands of Langerhans; diabetes in association with acromegaly may be referable to a lesion of the islands of Langerhans, namely, sclerosis and hyaline degeneration with adenoma-like hypertrophy.

In closing I wish to express my gratitude to Dr. Opie for much assistance and many valuable suggestions. I am indebted

to Dr. Thacher for twenty-one cases collected in his laboratory; to Dr. Wright for eighteen cases from the Massachusetts General Hospital; to Dr. Mallory for five cases from the Boston City Hospital and one case from the Long Island Hospital; to Dr. Libman for eight cases from Mt. Sinai Hospital; to Dr. Longcope for three cases from the Pennsylvania Hospital; to Dr. Oertel for six cases from the New York City Hospital; to Dr. Norris for two cases from Bellevue Hospital; to Dr. Adami and to Dr. Klatz for twelve cases from the Royal Victoria Hospital of Montreal; to Dr. Duval and Dr. White for five cases from the Montreal General Hospital; to Dr. MacCallum for five cases from the Johns Hopkins Hospital; to Dr. Wood for one case from St. Luke's Hospital; and to Dr. James and Dr. Stein for material from private cases.

#### *Discussion.*

DR. HARLOW BROOKS called Dr. Cecil's attention to the fact that he had described lesions in the islands of Langerhans in cases of acromegaly over ten years ago, one of which was a case of bronze diabetes. He thought that it was the general feeling that, while the islands of Langerhans were diseased in diabetes with remarkable constancy, still many marked lesions occurred in the islands quite independent of diabetes. He himself had never seen the parenchymatous changes so beautifully described by Dr. Cecil, but the other changes were seen with considerable constancy without diabetes.

DR. JAMES EWING said that he believed this report contained the largest proportion of cases with lesions of the islands of Langerhans yet recorded in connection with diabetes. In a considerable proportion of the cases the lesions found were those of the first group and were chiefly limited to the capsule of the islands. He would like to know if it were possible that such lesions could be sharply separated from those in the interstitial tissue. He had been interested in cases showing chiefly dilatation of the ducts and alveoli of the pancreatic parenchyma, lesions which were not illustrated in the sections shown.



DR. CHARLES NORRIS thanked Dr. Cecil for his able paper; he considered that his opinion was extremely valuable. His own experience had been confined to the examination of the pancreas in four cases of diabetes, but in all these he had seen hyaline changes in the islands of Langerhans. These changes were also present in cases of acromegaly, and were the only changes which were present. In the routine work at Bellevue Hospital, however, they saw constantly a large number of pancreases which showed more or less inter- as well as intralobular pancreatitis, without lesions of the islands of Langerhans and not associated with diabetes. In a large number of cases with arteriosclerosis there were also changes in the pancreatic vessels. In view of these facts, it would seem that these lesions were merely associated or frequently found in diabetes, and therefore not causative.

DR. THEODORE C. JANEWAY said that one great flaw in the explanations of the relation of pancreatic lesions to diabetes was the entire lack of any parallelism which most observers have noted between the severity of the disease and the extent of the anatomical lesions of the pancreas. He had seen four cases of normal pancreas associated with rapidly fatal diabetes. The most severe and most rapidly fatal diabetes was most frequently found associated with a normal pancreas; whereas the most pronounced changes were found in cases of diabetes occurring in older persons in whom such changes are more common apart from diabetes. There could be no question that there was a relation of some kind between the pancreas and the carbohydrate metabolism and diabetes; but the relation did not run in any way parallel with the course of the severity of the disease, was evidently a very complex one, and could not be solved by further anatomical studies of the pancreas, but must be reached from another side entirely.

DR. E. LIBMAN drew attention to one case, material from which he was under the impression he had given to Dr. Cecil. In that case there was marked hemosiderosis in the liver and spleen. In the pancreas there was no hemosiderosis, but there

was hyaline degeneration of the islands of Langerhans. The case was different from the type described by Dr. Opie in which there was hemosiderosis of the pancreas also, and in which he believed that the secondary changes resulting from the pigmentation were the cause of the diabetes.

DR. CECIL acknowledged his error as pointed out by Dr. Brooks. He said that, while lesions were very often found in the pancreas in cases which were not diabetes, these lesions were not found in the islands. He did not think that marked lesions of this sort were often found outside of diabetes. In regard to the large percentage of sclerotic islands noted, he had divided these into two groups: those in which the sclerosis was marked, and those in which it was not. Of course, in the latter group there would be a question whether the lesion was sufficient to interfere with the function of the islands. Thirty per cent. of his cases showed hyaline degeneration of the islands. There were certainly a number of cases included in the sclerotic group in which the lesions must be spoken of as moderate. He had not seen any dilatation of the alveoli except in one case, in a young woman about thirty-six years of age. In regard to the relation between the extent of the lesion and the severity of the disease, Dr. Cecil said that his clinical data were rather meager, and it had been hard to determine just how severe the diabetes had been; but he had found, as Dr. Janeway had said, that very often patients with an apparently normal pancreas, or with the least changes, ran a rapid course, and that with cases in older people where the lesions were more severe the course of the disease was longer.









SERIA

RB  
1  
N32  
n.s.  
v.7-8

New York Pathological Society  
Proceedings

**GERSTS**



